RISK ASSESSMENT

FOR THE COMBUSTION PRODUCTS OF

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL (MMT)

IN GASOLINE

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PREFACE

MMT, or methylcyclopentadienyl manganese tricarbonyl, is an organic compound which has been used in Canada since 1976 to raise the octane rating of gasoline. In 1977 MMT was banned for use in unleaded fuel in California because it was found to increase hydrocarbon emissions and to block the type of catalytic convertor then in use for unleaded fuel, thus negating the California program for dealing with the severe air quality problems of some California cities. Under the Clean Air Act, this ban was extended to all unleaded fuel in the U.S. in 1977. MMT remains in use in the U.S. in leaded gasoline.

In Canada, the phase-down and eventual phase-out in December 1990 of alkyl lead compounds as anti-knock agents and octane boosters, which began in the late 1970's, resulted in increased reliance on MMT for raising octane in unleaded gasoline. MMT provides only a limited amount of octane to Canadian gasoline: approximately 0.5 to 1 unit. In the U.S., octane needs have been met by changes in refinery production to increase aromatic content and/or branched chain hydrocarbon percentage, and also by the use of oxygenated fuels (ethanol, methanol, MTBE).

In 1978, in anticipation of the phasing out of lead additives in Canadian gasoline, the Department of Health and Welfare provided a review of the possible human health implications of the expected increase in the use of MMT, particularly with respect to effects on ambient air quality due to MMT-derived manganese (Health & Welfare Canada 1978). It concluded that there was "no evidence at present [based on data available in 1978] to indicate that expected ambient manganese concentrations would constitute a hazard to human health". During the course of their deliberations on lead additives and lead substitutes in gasoline, this question was re-examined in 1985 by the Royal Commission on Lead in the Environment. They arrived at a similar conclusion (Royal Society of Canada 1986). Health and Welfare Canada also commissioned two independent studies; one examined the updated toxicity database for MMT and manganese (Midwest Research Institute 1987), and the other completed an exposure assessment, including uptake of manganese, for various segments of the Canadian population (Hill 1988). The conclusions of both agreed with the earlier reports.

Ethyl Corp., the principal North American manufacturer of MMT, first applied to the U.S. EPA for a waiver of the prohibition on inclusion of new additives (including MMT) in American unleaded gasoline in 1977. This application, and a succeeding one in 1981 were refused on the basis that MMT increased hydrocarbon emissions and blocked catalytic convertors. A third application in 1991 was withdrawn due to a technical dispute with EPA over test results, and was resubmitted in July 1991. In January 1992, the EPA again ruled that MMT should not be allowed in fuel as it had led to substantially increased hydrocarbon emissions in tests by Ford Motor company over those seen in the extensive tests carried out by Ethyl Corp., and could lead to catalyst failure after long use (over 50,000 miles) (U.S. EPA 1992).

In this decision there was almost no mention of possible adverse health effects resulting from MMT use. However, there was an obvious concern among U.S. regulators over the issue of possible health effects from manganese, a metal additive, that might prove analogous to the lead experience. U.S. EPA public hearings heard extensive testimony on the health issues raised by MMT in connection with the 1990 waiver application by Ethyl Corp.. The U.S. EPA sponsored an international workshop in March 1991 to discuss research requirements for clearer delineation and quantification of possible exposure and adverse health effects due to manganese from automotive sources.

The primary health concern is not with MMT itself, but with the manganese oxides produced upon combustion of the additive. The known neurotoxicity of manganese at high (occupational) exposure levels has led to concern regarding its use as a gasoline additive, particularly given the recent experience with another metal, lead, in a similar capacity. The fear has been that, if MMT was used in all gasoline, ambient air manganese levels would rise sufficiently to cause central nervous system toxicity with Parkinsonian-like symptoms, as had been observed among workers exposed occupationally to manganese.

After the U.S. Court of Appeals accepted a petition for review of the 1992 denial decision, and after submission by Ethyl Corp. of additional extensive emission data to resolve earlier questions and conflicts, the U.S. EPA agreed to reconsider the decision for denial of MMT additives by November 1993. Based on these new data, in November 1993 the EPA ultimately concluded that MMT did not contribute significantly to increases in hydrocarbon emissions or failure of catalysts after extended service based on available data. The only question that remained was the issue of whether or not the use of MMT would present an unacceptable health risk to Americans.

During this same time period, the U.S. EPA examined several new epidemiological studies relevant to the establishment of an ambient level for manganese considered to have negligible health risk known as the Reference Concentration (RfC). A level of 1 μg Mn/m^3 for the RfC had been recommended in 1984 (U.S. EPA 1984), and of 0.4 μg Mn/m^3 in 1990 (IRIS 1993) when Ethyl Corp.'s current application was first submitted. This latter value was based on an epidemiology study of Belgian manganese factory workers (Roels *et al.* 1987a). The RfC was subsequently lowered to 0.05 μg Mn/m^3 in November 1993, immediately before the final decision on the waiver application was to be rendered, based on a new study by Roels *et al.* (1992) as well as the 1987 study and two additional similar studies in Sweden (Wennberg *et al.* 1991,1992) and Montréal, Canada (Mergler *et al.* 1994).

As there had been only limited opportunity for public comment on the new Reference Concentration as it was incorporated into EPA's reevaluation of the potential health risks associated with MMT usage, EPA agreed to resubmission of the MMT application by Ethyl Corp. and to re-review the basis for the new Reference Concentration taking into account comments received from Ethyl Corp. and others, as well as some additional original data from the principal study. A final decision was originally scheduled for May 30th, 1994, and was subsequently delayed to July 13th, 1994 (U.S. EPA 1993). In order to carry out the exposure portion of the risk assessment, the EPA undertook extensive investigations of possible exposure to manganese in the greater Los Angeles area, using modelling techniques as well as some actual measurements (Canadian ambient and personal exposure monitoring data were rejected for various reasons). On July 13th, 1994, the EPA announced that it would deny Ethyl Corp.'s waiver application on the grounds that there remain unresolved concerns regarding the health impact of manganese emissions produced by MMT use.

In light of the above, Health Canada undertook an independent risk assessment for the Canadian situation, focusing on the new epidemiological studies and Canadian exposure data.

CHAPTER I. MMT AND MANGANESE IN CANADA

I.1 MMT

Methylcyclopentadienyl manganese tricarbonyl (MMT CAS #12108-13-3) is an organometallic compound in which a covalent bond is formed between the cyclopentadienyl group and the manganese atom, and also between the three carbonyl groups and manganese. It has the chemical formula $C_9H_7MnO_3$ and a molecular weight of 218.1, with manganese comprising 25.2 percent of its total weight. It is liquid at ambient temperatures, and has a moderately low vapour pressure of 4.7×10^{-2} mm Hg @ 20°C. It has a water solubility of 70 mg/L @ 25°C and is soluble in hydrocarbon solvents (Health and Welfare Canada 1978; Dynamac 1983). The half-life of MMT in the atmosphere is extremely short, approximately 15 seconds, with photolysis leading to a mixture of manganese oxides (Ter Haar *et al.* 1975). This short half-life thus limits the chances of ambient exposure (Cooper 1984; Abbott 1987).

MMT is used in Canada in low concentrations as an octane improver and anti-knock agent in unleaded gasoline. The maximum concentration allowed is 18 mg Mn/l (Canadian General Standards Board 1986). Actual concentrations used have been considerably lower, ranging from 0 to 17.2 mg Mn/l for individual samples depending on the grade of gasoline, season, and geographical area (CPPI 1994), and the national mean was approximately 9 mg Mn/l in 1993. The data from a 1993 survey of manganese levels in Canadian gasoline are presented in Fig 1. By comparison, between 1981 and 1990, leaded compounds were added to gasoline in concentrations from 200 to 480 mg/L, over an order of magnitude above MMT (Environment Canada, in Loranger & Zayed, 1994a). Based on MMT sales in Canada (Wilson 1994), total annual manganese used in Canadian gasoline rose from 221 thousand kg in 1981 to 306 thousand kg in 1993. Again in comparison, total annual lead used in gasoline fell from 12 million kg in 1981 to 1.5 million kg in 1990 (11 months), the last year prior to the phase-out of leaded additives. MMT has also been used in very limited quantities worldwide as a smoke suppressant additive to fuel oils (Cooper 1984; Dynamac 1983).

MMT itself is considered to have a high systemic toxicity. It is also a confirmed genotoxic agent, and has recently been shown to cause a marked dose-related increase in structural chromosomal abberations, at MMT concentrations below those present in gasoline, in an *in vitro* test on CHO cells (Blakey 1994), thus indicating that it is a potent *in vitro* clastogen. This same laboratory is about to perform an *in vivo* micronucleus test to determine whether the clastogenicity detected *in vitro* is also expressed *in vivo*. If confirmed, this would indicate a more serious hazard than the *in vitro* results have shown.

Ambient exposure of the general population to unburned MMT appears to be extremely low. MMT was not detected in ambient air samples collected on the streets of Toronto in 1979, but was detected in an underground parking garage at a level of 0.1-0.3 ng/m^3 (detection limit 0.05 ng MMT/m^3) (Coe *et al.* 1980). Additional opportunities for exposure of the general public to MMT may arise during contact or through inhalation at self-service gasoline stations, through the use of gasoline as a solvent and cleaner, or as a result of substance abuse (gasoline sniffing). Unfortunately, there are no data available on the ambient levels of MMT at gasoline retail outlets or more recent ambient air monitoring data. Ethyl Corp. has reported traces (usually <0.1%, maximum 0.5%) of MMT in gasoline exhaust, apparently from cars not equipped with catalytic controls; emission control devices were reported to reduce this amount to 0.01-0.02 percent (Dynamac 1983). Exposure via evaporative emissions is also calculated to be low, due to the relatively low vapour pressure of MMT (5.0×10^{-2} mm Hg at 20□C) and the small amount used per litre (maximum allowable level of 18 mg Mn/l). The partial pressure of MMT in gasoline was calculated to be about 1/30 that of tetraethyl lead (Faggan 1975, in Dynamac 1983), and is an overestimate as the concentration per litre on which it was based (0.125 g/gal or 0.033 g/l) is three times the actual concentration used (Abbott 1987). Any MMT emissions that do occur are subject to a very short half-life (15 seconds).

There is a possibility of occupational exposure to MMT during the production process and during the blending and transferring of MMT. Since MMT is highly toxic, the manufacturer has recommended stringent precautions during this procedure. Few incidents have been reported of accidents; several accidents evidently occurred in the U.S. Navy during mixing of MMT with jet fuel, when seamen spilled MMT on their hands (Dynamac 1983). Occupational exposure to unburned MMT from skin contact with gasoline has not been reported as a problem, probably due to the small quantity per litre (approximately 40 mg/L of MMT). An occupational inhalation exposure limit value for MMT as manganese of 200 μg/m^3 (time weighted average) has been set by ACGIH (1993), with a skin notation, indicating that dermal exposure should be limited. To date, all of the MMT sold in Canada is manufactured in the U.S.: the majority of MMT is supplied by Ethyl Corp. from their plant in Orangeburg, South Carolina, and a small amount has been supplied by Sea Lion from their plant in Texas. Thus, occupational exposure within manufacturing facilities has not been an issue in Canada, although it presumably could be in the future. MMT monitoring data collected at Ethyl Corp.'s Orangeburg plant (provided by Pfeiffer, 1994) for areas with various MMT-related activities indicate organic manganese concentrations below detection limit (0.05 mg/m^3) for most samples and a range of 0.05-0.120 mg/m^3 in samples above the detection limit. MMT produced by Ethyl Corp. in South Carolina is blended with a solvent at an Ethyl Canada Inc. plant in Corunna, Ontario prior to distribution to refineries. Limited personal and stationary air monitoring of

MMT levels for MMT blending unit operators from 1990-1993 found all levels to be below the detection limit which itself was relatively high (0.1 mg/m^3 as manganese in all but one sample and 0.2 mg/m^3 in one sample).

Due to a lack of potential for exposure, the risk to health from MMT was previously considered to be minimal. A very recent (as yet unpublished) investigation shows that MMT is a potent clastogenic agent at concentrations below those present in Canadian gasoline, which indicates that some caution is required in considering whether the addition of this genotoxic compound to such a widespread consumer product is justified. Although exposure of the general public appears to be low, some potential exists for exposure through abuse (gasoline-sniffing) or through use of gasoline as a solvent and cleaner. Improper use of a substance is difficult to control; drastic action is seldom contemplated unless such use is extremely widespread or has additional effects on the general population or on the environment. Moreover, the toxicity of the gasoline itself under these circumstances is higher than that of MMT.

Occupational exposure to carcinogenic, genotoxic or neurotoxic substances is common, and control measures for limiting such exposures are normally effective at the level of the workplace, rather than at the national level, or by banning the compound from commerce.

I.2 Manganese

Manganese (Mn) is the twelfth most abundant element in the earth's crust, comprising approximately 0.1%, and the fifth most abundant metal (ATSDR 1992; U.S. EPA 1984). It is widely distributed in rocks, soil, food, water and living organisms (WHO 1981). Manganese occurs naturally as a component of sulphide, oxide, carbonate and silicate minerals, and is most common in the manganese ores pyrolusite (MnO_2), rhodochrosite ($MnCO_3$) and rhodanate (manganese silicate) (ATSDR 1992; Jaques 1987; Stokes *et al.* 1988). Manganese does not occur as a free metal, but rather it is found in nature in 11 oxidation states, the most important of which are Mn^{2+}, Mn^{3+}, Mn^{4+}, and Mn^{7+}. Mn^{2+} salts, eg. $MnCl_2$, $MnNO_3$, $MnSO_4$ and Mn acetate, are mostly water soluble, with the exception of the phosphate and carbonate which have a relatively low solubility. The Mn^{2+} ion is similar to magnesium, Mg^{2+}, and can replace it in some biological systems. The oxides, including Mn_3O_4 and MnO_2 (manganese dioxide or pyrolusite -Mn^{4+}) are insoluble in aqueous solutions. The Mn^{3+} ion is relatively unstable in the environment and hydrolyses easily in weak acid solutions to Mn^{2+} and MnO_2 (Mn^{4+}) (WHO 1981). In biological systems, the Mn^{3+} ion acts interchangeably with Fe^{+3} (Aschner & Gannon 1994).

The principal product of combustion of MMT in gasoline is inorganic manganese, in the form of airborne particles of trimanganic tetroxide, (Mn_3O_4), along with traces of manganese sesquioxide (Mn_2O_3) (Ter Haar *et al.* 1975; Health and Welfare Canada 1978). It is a mixed oxide, in which two manganese atoms exhibit the valence state of +3 and one exhibits the state of +2. The particle size is between 0.2 and 0.4 μm, small enough to reach the lung alveoli and to be absorbed easily. Mn_3O_4 has a molecular weight of 228.8, of which 72 percent is manganese. It is insoluble in water or in biological fluids, but is soluble in hydrochloric acid. Mn_3O_4 is also a naturally occurring mineral known as hausmanite (the size of manganese particles of crustal origin tend to be much larger than those produced anthropogenically).

The U.S. EPA conducted multiple emission tests on 12 vehicles using three drive cycles (FTP, HWY and NYCC) in order to measure manganese emissions. The average amount of the MMT-derived manganese emitted from the tailpipe ranged from 6.6-16.9% depending on the drive cycle, with an average of 12.5% (Systems Application International 1991). The minimum and maximum cycle means were 4.2% and 33.7%, respectively. In addition, Ethyl Corp. and the Southwest Research Institute carried out an emission study entitled *The Manganese Balance Project* (Ethyl Corp. 1991). Three 1991 Chevrolet S-10 pickup trucks were tested after accumulation of 20000 miles on a base gasoline with MMT at a level of 8 mg Mn/l. Analyses showed that under these conditions 26-28% of the manganese consumed in the fuel was emitted from the tailpipe, while the majority of the balance was found within the internal components of the vehicle (approximately 40% in the tailpipe, muffler and catalytic converter; 12% in the engine oil and filter; and 15% in the engine parts). Retrieval of a small total mass (17 grams) of manganese from the internal components was difficult and a certain percentage remained unaccounted for. A five vehicle, low mileage study by Ethyl using three drive cycles measured manganese emission rates ranging from 4-19%, and a 4 vehicle (low to high mileage) study by Ford (FTP drive cycle) measured manganese emission rates of 8-45% (U.S. EPA 1994). An older study by Ter Haar *et al.* (1975) found that 20% of fuel manganese was emitted in the exhaust of two vehicles (unequipped with catalytic converters). An additional study of non-catalyst equipped vehicles report emission rates ranging from 11-40% (Moran 1975, as reported in U.S. EPA 1994). Given the limited testing done to date, the lack of testing of on-road vehicles, and the great variability in the data, it is not possible to determine a statistically valid manganese emission factor for the current vehicle fleet. This document will assume that 40% of manganese added to gasoline as MMT is emitted from the tailpipe. (Note that this emission factor is not used in the exposure assessment.)

An ambient air quality guideline of 1 μg Mn/m^3 has been recommended for Europe (WHO 1987). The U.S. EPA Reference Concentration of 0.4 μg Mn/m^3 established in 1990 was reduced to 0.05 μg Mn/m^3 in 1993: the recent EPA assessment of MMT proposes that the

RfC be a range of 0.09-0.2 μg Mn/m^3 (U.S. EPA 1994). The province of Ontario has a 24-hour criterion for manganese of 2.5 μg/m^3 in total suspended particulates based on human health (OMEE 1993). An occupational TLV of 5 mg Mn/m^3 of manganese dust and inorganic compounds is used by ACGIH (1993), although a new value of 200 μg Mn/m^3 has been proposed.

I.3 Anthropogenic Sources of Manganese in Canada

Manganese ores are not mined in Canada but are imported for various industrial purposes. Anthropogenic manganese emissions in Canada are derived primarily from metallurgical processing (such as manganese alloy production), and steel and iron manufacturing. However, fuel combustion in both stationary and mobile sources also results in the release of manganese to the atmosphere, the primary source of manganese from vehicular fuel combustion being MMT (methylcyclopentadienyl manganese tricarbonyl).

The most recent comprehensive anthropogenic emissions inventory analysis for manganese in Canada was compiled for 1984 (Jaques 1987). These data are presented in Table 1 for the individual provinces and for the country as a whole. It is evident that national manganese emissions are centred in Québec and Ontario, and result primarily from manganese-bearing alloy production and primary iron and steel production in those provinces, respectively, and were responsible for 47 and 28 percent of national manganese emissions, respectively. (It should be noted that a large manganese alloy production plant in Beauharnois, Québec, 24 km SW of Montréal, closed in May 1991.) Transportation related fuel combustion is a principal source in the other provinces and territories, representing one third to all of the anthropogenic manganese emissions in those regions. In his analysis, Jaques (1987) assumed a tailpipe emission rate of 100%: as discussed in the previous section, evidence from emission tests indicates that less than 40% of the manganese in fuel (manganese represents 25.2% of MMT by weight) is emitted from the tailpipe.

This inventory has not yet been updated, however, data are available on changes in MMT sales since that time from Ethyl Corp., who has been the sole or primary supplier of MMT in Canada since the early 1980's. Sales of manganese sold as MMT in Canada (by Ethyl Corp. alone) from 1981 to 1993 are provided in Fig. 2. MMT/manganese sales at Ethyl Corp. have increased by approximately 40% from 1984 to 1993, and by 93% from 1984 to 1989. Assuming a tailpipe emission factor of 40%, annual manganese emissions from the transportation sector have increased from 88 tonnes in 1984 to 122 tonnes in 1993, with a peak of 168 tonnes in 1989 (note that these estimates differ from Jaques (1987) because he assumed that 100% of manganese in gasoline was emitted from the tailpipe). Given these figures and assuming (probably incorrectly) that emissions from other sectors have remained constant, gasoline-powered motor vehicles represented 9%, 17% and 12% of anthropogenic manganese emissions in Canada in 1984, 1989 and 1993, respectively. It should be noted that unlike point-source industrial emissions, motor vehicle emissions are widely distributed in the environment, and thus may contribute more substantially to the manganese exposure of the general population than the emissions inventory data suggest.

CHAPTER II. PHARMACOKINETICS OF MANGANESE

The metabolism of manganese is of unusual importance in the risk assessment for manganese from MMT. Questions have arisen regarding differential metabolism and homeostasis of inhaled versus ingested manganese, possible differences in toxicity between the various forms of manganese, and the effects of exposure on different subpopulations (the very young and the elderly), which are best answered by the study of the metabolism of this element. Inhalation is the important route of exposure for consideration with respect to a risk assessment of the use of MMT in fuel, and also in cases of occupational exposure to manganese, while normally the gastrointestinal route is the major port of entry into the body for manganese.

II.1 Absorption

II.1.1 Inhalation exposure

Net absorption after inhalation is a combination of deposition and uptake of deposited particles. Absorption via inhalation is strongly dependent on the form and size of the manganese-containing particulate matter. Deposition of all particulate matter in the lower respiratory tract occurs only with particles □10 µm in mass median diameter. It has been assumed for the purposes of this assessment that 60% of particulate mass for particles of diameter less than 10 µm is deposited in the pulmonary region of humans and is available for uptake. This is likely a conservative estimate, as published data indicate that 60% deposition is a maximum value and applies to particles between 3 and 5 µm mass median aerodynamic diameter (MMAD), and that deposition is substantially lower for particles less than 3 µm and for particles 5-10 µm (U.S. EPA 1982). Deposition drops to about 20% for particles 0.5-1 µm in size, and increases up to a maximum of 60% for particles of 0.1 µm (U.S. EPA 1984). A more recent review of this information (Oberdorster *et al.* 1994) supports this conclusion. Particles 2-3 µm or less are small enough to be deposited in the lung alveoli where clearance mechanisms are slower than for tracheobronchial clearance via ciliary action, and thence to the gastrointestinal tract after swallowing. The particle size of Mn_3O_4, the major oxide produced upon combustion of MMT, is about 0.1 to 0.4 µm (Ter Haar *et al.* 1975), small enough to reach the lung alveoli easily, but also small enough to experience considerable loss through reentrainment and immediate exhalation (U.S. EPA 1984). There is very limited information on particulate deposition in children, however, Xu and Yu (1986) modelled alveolar deposition of different particle sizes for different ages and found that although alveolar deposition may be higher or lower in adults than children, all PM_{10} size fractions have deposition below 60% in all age groups. It has also been assumed that 100% of manganese deposited in the pulmonary region is absorbed into the circulatory system and is available to induce toxic effects, as a conservative estimate, since data indicate that uptake of deposited particles, although variable, can range up to 90 percent based on retention data. The net absorption, including deposition and uptake has therefore conservatively been assigned a value of 60 percent for this assessment.

II.1.2. Gastrointestinal route

Because of the normal high amount of manganese in the diet, this constitutes the major route of exposure for most people (Mena 1980). Absorption via the GIT is normally at least an order of magnitude lower than via the inhalation route.

It is hypothesized that manganese homeostasis is regulated by manganese excretion via the intestinal tract rather than absorption (Davidsson *et al.* 1991). However, the knowledge of manganese absorption (as opposed to retention) is limited, and is complicated by relatively rapid and efficient biliary removal (Sandstrom *et al.* 1990). In the normal (human) adult, absorption of radiolabelled $MnCl_2$ via the oral route was about 3% of the ingested dose and remained constant as intake increased (Mena 1980). Absorption from the gut also remained constant at 3% with increased loads of Mn up to 5000 $\mu g/m^3$ from occupational exposure of manganese miners. Manganese absorption and retention from human milk, cows' milk, and various formulas were studied in 39 adults (Davidsson *et al.* 1989a). Absorption was 8.9 % from human milk, 2.4% from cows' milk, and 0.7% from soy formula. Protein composition, iron levels, and phytic acid (in the soy formula) all influenced absorption. Absorption from milk and from a multi-vitamin solution was 8.4 and 8.0 % in a human volunteer study (Sandstrom *et al.* 1987). In a review of the literature, Hill (1988) derived a mean estimate of manganese absorption for adults of 5.5% based on a range of 1-14.5%. This is similar to the mean value proposed by ATSDR (1992) of 3-5%. Although manganese absorption from a constant diet is fairly reproducible within an individual, inter-individual variation can be substantial (Davidsson *et al.* 1989b; Davidsson *et al.* 1991), which may be partially responsible for the variability in published estimates. Results from additional studies include: 1.2-4.9% (Davidsson *et al.* 1991), 1.7-5.2% (Johnson *et al.* 1991) and 0.7-8.2% (Davidsson *et al.* 1989a) for different dietary components; 6.05% (Davidsson *et al.* 1989b); and 2% from a mineral supplement taken with food and 9% from that supplement taken in a fasting state (Sandström *et al.* 1987). Absorption in laboratory animals is also of the order of a few percent, similar to humans (Cahill *et al.* 1980; Van Barneveld & Van den Hamer 1984).

For the purposes of this assessment, a value of 5% has been selected as adult manganese absorption from the gastrointestinal tract.

Low iron status results in increased absorption of manganese. Individuals with anaemia absorbed about 7.5% , or twice as much manganese as normal individuals, along with greatly increased absorption of iron (Mena *et al.* 1969; Mena 1980). In one study, one of 14 volunteers, who was anaemic, had an absorption of 45%. (Sandstrom *et al.* 1987). This has also been shown in animal studies. In iron deficient rats, manganese binding to transferrin was increased by 100 %, as was also the specific activity of labelled manganese in brain stem, basal ganglia and medulla (Mena 1974). Iron and manganese in the diet interact, so that high levels of one depresses absorption of the other (Hurley *et al.* 1983). High calcium levels also reduce the absorption of manganese in humans (Davidsson *et al.* 1989a) and rats (Van Barneveld & Van den Hamer 1984). As with several other metals, absorption of manganese from water may be increased over absorption from food; the apparent absorption of manganese in mice following administration of 0.3 ug ^{54}Mn in either food or drinking water was 1 percent from food compared to 5.3 percent from water (Van Barneveld and Van den Hamer 1984).

Infants have a greatly increased absorption and retention capacity for ingested manganese compared to adults. Mena (1980) quoted 15.7% and 8% as the 10-day total retention in premature and normal full term infants respectively. In a manganese balance study (Zlotkin and Buchanan 1986) on premature (N=11) and full-term infants (N=13) intravenously fed either a manganese-deficient (0.8 µg/kg bw/day) or a manganese-supplemented (48 µg/kg bw/day) solution, obligatory excretion was extremely low, less than 1 µg/day, in all four groups. Manganese retention was 99% for the exposed group and was unaffected by gestational age, birth weight, or other factors. Mean plasma levels were the same at 640-42 ng/ml for both groups. Three of 13 infants in the unsupplemented group were in negative balance at -0.7 µg/kg bw/day. Although there were no detectable differences in neurobehavioural function, the authors recommended that parenteral manganese supplementation be carried out primarily for premature infants, based on a 9 µg/kg bw/day accretion rate for fetuses in the third trimester, in order to avoid a negative balance, and at the much lower rate of 1 µg/kg bw/day for full-term infants. The mean retention of manganese in infants fed human milk or cows' milk was reported to be 43% and 20% respectively (the age of the infants not given) (Doerner *et al.* 1987). Infants of other species also demonstrate greater absorption and retention. Infant rats had a four-fold increased entrance of labelled manganese into the brain compared to adults (Mena 1974), and young rats also showed a pronounced inverse effect of age on the whole-body retention of manganese, with 24-hour retention 80% in rat pups less than 15 days old, and 40% in pups over 15 days old. (Keen *et al.* 1986; Raghib *et al.* 1987). This higher retention appeared to be due to inefficient excretory mechanisms rather than to increased absorption, based on results from an *in vitro* study on membranes from the small intestine of 14-to 21-day old (weanling) rats (Bell *et al.* 1989). Davidsson *et al.* (1989a) have suggested that the high capacity for manganese absorption and retention in young infants is a consequence of the scarcity of this essential element, and that this is therefore a conservation mechanism to prevent deficiencies, which have been shown in animals to result in disturbances of development (Hurley *et al.* 1983). Suggestions have also been made that deficiencies in manganese during infancy have resulted in increased prevalence of seizures in humans (Tanaka 1982; Papavasiliou *et al.* 1979), but this does not agree biologically with the virtually 100% retention of human infants, and the difficulty of establishing a deficient state, in either adults or the young. In a later epidemiology study to further investigate a possible link between seizures and body manganese levels, Dupont and Tanaka (1985) suggested that seizure activity could be enhanced by low or borderline manganese status, combined with seizure-induced alterations in permeability of the blood brain barrier, which allowed the excessive egress of manganese from the neuron. In a group of 197 convulsive children from a hospital clinic aged one to 19 years, 14 percent had blood manganese levels two standard deviations below the mean of 120 control children.

For the purposes of this assessment, it has been assumed that infants absorb 100% of manganese from the diet.

II.2. Tissue Distribution and Retention of Manganese

II.2.1 Inhalation exposure

Immediately following inhalation of 1,800 µg/m^3 (□260 µg/kg bw/day) Mn$_3$O$_4$ for 2 hours by female mice, tissue distribution was highest in lungs, followed by liver, kidney and spleen (Adkins *et al.* 1980). After 48 hours, lung tissue levels had fallen close to levels seen in the controls, while kidney and spleen levels were still elevated 60% above controls. Pulmonary deposition was linear with dose from 0 to 2900 µg/m^3 for the same exposure period. Liver tissue levels were slightly but not significantly elevated from the control level at 48 hours. Brain levels were not measured in this study . Acute exposure of guinea pigs to considerably higher concentrations of MnO$_2$ (22,000 µg/m^3) for 24 hours resulted in lung retention of 27% after 24 hours (Bergstrom 1977). A one-hour nose-only inhalation exposure (Wieczorek and Oberdorster 1989) of male rats to 2.9 and 129,000 µg/m^3 MnCl$_2$ (mean size 1.1 to 1.6 µm) resulted in the highest manganese levels in the gastrointestinal tract (87% of the total absorbed for the high dose and 62% for the low dose) immediately after exposure, followed by lung, liver, and kidney, with extremely low brain levels, 0.1 µg and 0.001 µg compared to 575 µg and 13.6 µg in the gastrointestinal tract (GIT) for the high and low dose respectively. Deposition patterns were similar for both the high and the low dose. The relative uptake into the brain was independent of inhaled concentration and did not exceed 1% of lung deposition. The large quantity and rapid appearance of manganese in the GIT in this experiment suggest that the homeostatic mechanisms which act through the GI tract and liver to control manganese levels after oral intake, also remove a significant portion of absorbed manganese after inhalation intake.

Moore *et al.* (1975) exposed rats and hamsters to auto exhaust from an engine run on gasoline containing MMT, with average Mn (presumably Mn_3O_4) measured at 117 $\mu g/m^3$, for 56 days, 8 h/day. No significant differences were found in the Mn concentrations of various tissues between controls and exposed groups of hamsters (no explanation of this finding was attempted), but in rats, concentrations rose 60-75% in brain, lung and liver, and remained low in kidney and heart (Moore *et al.* 1975). After subchronic inhalation exposure of rats and monkeys to 12, 112 and 1150 $\mu g/m^3$ Mn_3O_4 (produced from combustion of MMT) continuously for 9 months, the highest tissue manganese levels were in the liver in both species, but were not significantly elevated in the liver above controls for any exposure group (Ulrich *et al.* 1979). Blood, kidney and lung levels were somewhat elevated in the two higher dose groups in rats and monkeys, which also had elevated spleen levels. Tissue and blood manganese levels in the highest dose group were increased 34 to 125% above the control values and were generally comparable between rats and monkeys. Exposure at the lowest dose, 12 $\mu g/m^3$, had no effect on manganese levels in any tissue. In rats, levels had returned to control values six months after the cessation of exposure. Brain levels were not investigated in this study . In male mice subchronically exposed to sublethal doses of manganese dioxide, MnO_2, (mean size 1.5 μm) at 49,000 $\mu g/m^3$ for 3 to 12 weeks, followed by 85,000 $\mu g/m^3$ for 20 weeks, uptake of manganese was highly significant ($p<0.001$) in lung,kidney, cerebrum, brainstem, liver, and blood, as well as the gastrointestinal tract and testes ($p<0.01$), immediately following the beginning of exposure (Morganti *et al.* 1985). The increase was transient, however, and levels dropped comparable to controls, in blood, lungs, cerebrum and brainstem as exposure continued beyond 24-28 weeks (20 weeks for blood). Mn remained elevated in liver, even 2 weeks after cessation of exposure, when all other tissue levels including cerebrum and brainstem, had reached control values . This was suggestive of a prominent role for the liver in controlling body burden of inhalation-derived as well as GIT-derived manganese through biliary excretion.

Other routes of parenteral administration have also been examined. Administration to rats via subcutaneous injection of MnCl2 at 15 mg/kg bw/day for 15 days resulted in increases in total manganese in all tissues (Sakurai *et al.* 1985). The increases were most marked in pancreas, 2800 percent over control levels, and were also high in testis (1300%), hypophysis (650%), thymus, adrenal,and cerebrum (all 600%). Content in liver, thyroid and lung increased relatively little over levels in controls. In the controls, levels were highest in thyroid and liver, and were due solely to uptake from standard laboratory chow and from drinking water. Gianutsos *et al.* (1985) also observed increased levels of manganese in the blood and in brain of mice following a single subcutaneous injection of approximately 22 mg/kg bw of either $MnCl_2$ or Mn_3O_4. Blood levels were 100 times control levels in one hour after the chloride, dropping to 7 times after 7 days, whereas with the oxide, the blood level doubled after two hours and remained high to the end of the experiment at 7 days. Brain levels increased steadily to 7 days after administration of both compounds, with more rapid accumulation from the chloride, but more than twice the accumulation from the oxide at the end of 7 days. Iron deficiency increased the retention of manganese in the brain stem, basal ganglia, and medulla of rats, by approximately twice (Mena *et al.* 1974). *In vitro*, the Mn-binding capacity of plasma was increased significantly from 21 to 48 percent when iron was low.

II.2.2 Gastrointestinal route

In human adults, whole body retention of an orally ingested dose was reported to be 1.6% after 10 days and 0.21 % after 50 days (Mena 1980). In the newborn, total body retention was 8%, while premature infants retained twice as much (the length of time was not given for the infants). In rats, whole body retention of a single ingested dose at day 19 post-partum was 3%, similar to adult retention (Cahill *et al.* 1980). Twenty-four hours following the end of subchronic (100 day) administration of four different manganese salts to six-week-old male mice at about 200 mg/kg bw/day, the manganese content in body tissues increased 1.4 to 3 times over that in controls, varying only slightly between forms (Komura and Sakamoto 1991). Manganese content was highest in liver, kidney and hair, followed (in order) by pancreas, bone, prostate, brain, spleen and muscle. Manganese content in brain averaged 1.4 to 1.6 µg/g (tissue wet weight) for the four forms, compared to 0.97 ± 0.25 µg/g in control animals, and was significantly higher for the acetate form only. In a longer (1 year) study using the same protocol, increases in manganese content of the liver, kidney and spleen were not as marked (with few increases statistically significant), as in the shorter experiment, due to homeostasis, according to the authors (Komura and Sakamoto 1992). The insoluble carbonate caused a significant elevation over the control level in the liver and spleen, and the oxide in the spleen only. The elevation by the oxide in the spleen was significantly higher than the other three forms. The manganese content in seven areas of the brain varied slightly from control values between the various forms, whether soluble ($MnCl_2$, Mn acetate), insoluble (Mn carbonate, MnO_2), tetravalent (the oxide) or divalent (the three remaining forms), but no particular pattern was discernible with respect to the solubility or the valence state. MnO_2 caused significant decreases over control levels of dopamine and norepinephrine in the corpus striatum, hypothalamus and midbrain, which led the authors to conclude that this form was more toxic than the other forms. However, these decreases were not correlated with any increases in manganese levels in these tissues as might have been expected. In addition, dopamine levels were doubled in the cerebral cortex, cerebellum and medulla oblongata while Mn levels were unchanged or even increased in the cerebral cortex (Komura and Sakamoto 1992).

II.3 Clearance of Manganese

II.3.1 Inhalation exposure

Highly variable clearance of manganese from the lung has been reported after inhalation exposure. Overall lung clearance values ranged from <3.5 hours in female mice (Adkins *et al.* 1980) to >240 days in male rats (Kalliomaki *et al.* 1986). Clearance half-time ($T_{1/2}$) in humans was reported to be 68 days for MnO_2 particles of 0.9 µm mass median diameter (MMD) (Morrow *et al.* 1967). Clearance was generally reported as bi- or triphasic in animals, with initial fast and later slow components.

Lung clearance appears to be inversely dependent on concentration. Much faster clearance (0.2 d vs. 1.8 d or 9-10 times) was observed (Wieczorek & Oberdorster 1989) in the first or rapid phase of clearance in male rats given 129,000 µg/m3 soluble $MnCl_2$ than in the group given 2.9 µg/m3. The late phase clearance rates were more nearly equal with clearance half-times ($T_{1/2}$) of 10.5 and 12.7 days for the high and low concentrations respectively. (Particle sizes were 1.6 and 1.1 µm mass median diameter (MMD), which may have also influenced the half-time). Lung clearance of $MnCl_2$ aerosol, MMD 1.1 and 1.8 µm, was triphasic in two macaque monkeys administered extremely low doses of 0.01 and 0.02 µg Mn (0.003 and 0.008 µg/kg bw) intratracheally for 30 minutes (Newland *et al.* 1987). Disappearance half-times were 0.2-0.4 d, 12-26 d, and 94-187 d for the 3 phases. This extremely slow clearance of low doses agrees well with the observations by Wieczorek & Oberdorster (1989) of inverse $T_{1/2}$ for low concentrations.

Differing particle size may explain some of the differences in clearance rates observed in various studies, some of which used intermediate particle sizes between 1.1 and 1.9 µm diameter. Mn_3O_4 resulting from auto combustion is noted to be of small particle size, 0.2-0.4 µm. Small particle sizes are likely to clear more slowly than larger particle sizes, which are cleared by mucociliary clearance largely to the GIT. Bergstrom (1977) explained the difference between his rapid 24-hour lung clearance half-time in guinea pigs of MnO_2 particles, all >0.8 µm and 87% <3 µm, and the slow ($T_{1/2}$ of 38 days) clearance observed by Morrow *et al.* (1967) in dogs, on the basis of larger size than the particle of 0.07 µm count median diameter used in the dog study. The short half-time of < 3.5 hours observed by Adkins *et al.* (1980) for female mice given a Mn_3O_4 aerosol of 1.4 µm MMAD appears to be an anomaly. The experiments of Kalliomaki *et al.* (1986) on lung clearance of manganese from metal fumes are of interest with respect to possible differences due to particle size. Lung clearance was extremely slow with $T_{1/2}$ of 107 days overall and 140 days for the slow phase, for inert gas-stainless steel fume, with the size not given, but probably in the ultrafine range << 0.1 µm. (This was fairly similar to clearance of iron and chromium in the same fume at a $T_{1/2}$ of 240 days.) Ultrafine particles of other metals (eg. titanium and aluminum) have also been observed to give extremely long clearance times due to phagocytosis of particles by alveolar macrophages and translocation into the pulmonary tissue (Ferin *et al.* 1991). Larger size manganese particles from two other types of metal fumes from manual metal arc welding, also investigated by Kalliomaki (Kalliomaki *et al.* 1986), gave lung clearance $T_{1/2}$ of 0.5 an 5.0 days for fast and slow phases from mild steel fume, and 5.0 and 40 days from stainless steel fume, the latter said to be between 0.3 and 0.6 μm, with some aggregation into chains of several μm in length (Kalliomaki *et al.* 1983).

The form (soluble or insoluble, oxide or other salt, Mn^{2+}, Mn^{3+}, Mn^{4+}) in which the Mn occurs also appeared to influence clearance in a study (Drown *et al.* 1986) in which $MnCl_2$ (soluble salt) or Mn_3O_4 (insoluble oxide) were both administered intratracheally at low dose. The soluble $MnCl_2$ was cleared four times faster during the first week after administration than Mn_3O_4, but by the end of 15 days, no further lung clearance took place for either compound and lung concentrations were the same. Mn uptake by all other tissues was also more rapid with the $MnCl_2$ form, and peak concentrations were reached earlier.

Translocation of particulates deposited in the respiratory tract via ciliary action and swallowing to the gastrointestinal tract is a major clearance mechanism for respiratory exposures (ICRP 1966). Mena *et al.* (1969) demonstrated that humans inhaling a suspension of particulate manganese oxide ($^{54}Mn_2O_3$) transferred more than 60% to the gastrointestinal tract; this is likely true also for Mn_3O_4 particles of equivalent size.. Pre-systemic clearance or the "first-pass effect" is generally considered to account for part of the large difference in apparent toxicity between ingested and inhaled manganese. In ingestion, the liver acts to extract Mn rapidly from the blood, followed by excretion into the bile and elimination via the faeces. $MnCl_2$ administered portally to rats was only 65 to 70 percent of that available systemically (intravenously) (Thompson & Klaassen 1982). A major portion of inhaled manganese also appears to be found in the liver shortly after inhalation (Adkins *et al.* 1980; Wieczorek & Oberdorster 1989), indicating that clearance via the GIT is also important in inhalation exposure, particularly for high doses. Drown *et al.* (1986) found that a total of approximately 60 and 73 percent of intratracheally administered Mn_3O_4 or $MnCl_2$ respectively was excreted via the GIT. The remaining 25 to 40 percent is, however, very important with respect to potential brain toxicity.

Clearance from the brain, the critical target organ, appears to be extremely slow once manganese has reached it. Mena *et al.* (1974) reported that the entrance of manganese into the brain was a slow process in normal rats, reaching a maximum of 1 percent 30 days after ip. injection, followed by slow clearance with a half-time of 150 days. Newland *et al.* (1987) estimated clearance half-time for the brain to be 223-267 days for macaque monkeys given ultra-low concentrations of $MnCl_2$ aerosol. Wieczorek & Oberdorster (1989) also found that although maximum uptake by the rat brain was less than 1% of uptake from the lung for both high and low concentrations, brain clearance was too slow to calculate after 120 days; clearance was even slower after administration of low concentrations than for higher concentrations. After intratracheal instillation of small amounts of $MnCl_2$ and Mn_3O_4 in rats, maximal concentration were attained at 1 day ($MnCl_2$) and 3 days (Mn_3O_4) and a second peak was observed at two weeks for both (Drown *et al.* 1986). The clearance half-time appeared to be approximately 60-70 days, with brain concentration returning to baseline by 90 days. This slow clearance for brain is seen when Mn is administered via other routes also. For humans, Mena (1980) gives a clearance half-time for the head of 54 days in normal individuals, 37 days in manganese miners, and 62 days in sick Mn-exposed miners, after injection of radioactive ^{54}Mn. This suggested that slow clearance (for genetic or other reasons) could be at least partly responsible for the variability in susceptibility to the toxic effects of manganese noted in occupational studies. Divalent manganese, which is found in brain mitochondria in extremely small amounts, has been shown to share the same entry mechanism as calcium, but to lack the Na^+-dependent efflux mechanism of calcium, and therefore to exit extremely slowly (Gavin *et al.* 1990), thus providing one mechanistic reason for slow brain clearance.

II.3.2. Gastrointestinal route

After ingesting manganese in the diet or in a multivitamin solution, whole-body clearance in 14 volunteers was biphasic, with clearance half-times of 13 and 34 days for the fast and slow components (Sandstrom *et al.* 1986). In two of these subjects later followed after intravenous dosing, half-times were faster than average in one individual (8 and 15 days), and slower in the other (23 and 65 days). The whole-body clearance for normal individuals, not occupationally exposed, was reported to be about 10.5 days for oral exposure, compared to 37 days for exposure via injection (Mena 1980). Dastur *et al.* (1971) reported that the elimination half-time of manganese was 95 days in monkeys; brain levels were still high after 9 months. In mice, the whole-body clearance of radiolabelled manganese after administration of $MnCl_2$ at 20 to 2000 µg/L in drinking water for 26-30 days varied from 6 days for the low concentration of 20 µg/L to 1.0-1.5 days for the high concentration of 2000 µg/L (Suzuki 1974). Also in mice, the half-time for the fast phase of elimination was less than 1 day following an oral dose of 0.3 µg Mn, and was 8.4 days for the slow phase, at low doses, both parenterally and orally (Van Barneveld and Van den Hamer 1984). After oral administration of 0.14 µg $MnCl_2$ to mice, clearance was triphasic; 90% was lost within the first day in the excretory phase, and the half-times were 2.5 and 19 days for the other phases (Strause *et al.* 1985). In 24-day old rats (weanlings), the overall clearance half-time for manganese sulphate administered in the diet was less than 19 hours, and the manganese content of the GIT itself was $\leq 0.1\%$ of the administered dose after 16 hours (Rehnberg *et al.* 1985). By contrast, the clearance half-time in 10 day old infant rats was

107 hours. Low iron status facilitated retention. Uptake by the brain of gavage-administered $MnCl_2$ (75-150 mg.kg bw/day) in weanling (20 day old) rats peaked at 5 days, at one-third the amount in 3 and 10 day old rats (Heilbronn *et al.* 1982). Clearance from the brain was complete by 14 days, whereas in the infant rat brain, appreciable amounts remained, 1/4 to 1/3 the original uptake, after more than seven weeks. Reported whole-body clearance times for rodents appear to be faster than for humans or other primates, after oral intake. Therefore some caution is required in extrapolating clearance results from non-primates to humans.

II.4 Inhalation versus Ingestion Exposure

The route of exposure, via inhalation or via the gastrointestinal tract, is of great importance in considering the potential toxicity of manganese to humans with respect to its concentrations in the environment. Potential differences in toxicity arise from differences in the metabolism and handling of manganese after it enters the body either through the gastrointestinal tract (GIT) or through the lungs and also via other parenteral routes such as the intravenous and subcutaneous routes. Under normal circumstances, virtually all manganese enters the body via the oral route. Several mechanisms act to ensure that toxic concentrations are not reached if oral intake is high. Absorption via the GIT in humans is somewhat variable, but on average is around 3 to 5 percent of intake, independent of increasing amounts. A major homeostatic mechanism is provided by biliary excretion via absorption and processing through the liver, with elimination in the faeces. Based on the high concentrations concentrated in the liver after oral intake, the vast majority of elimination takes place by this route, accounting for approximately 60-90% of uptake. Net retention is therefore quite low, on the order of 1 to 2 percent after a few weeks, and possibly much less than 1 percent over the long term, based on the extremely low body burden (0.17-0.29 μg/g) found in adults after many years of high dietary intake in the order of several milligrams per day (ICRP 1975; WHO 1981). At excessive concentrations, this mechanism becomes less efficient, and increasing amounts of manganese may be released for systemic distribution to the tissues. Toxic effects on the central nervous system have been observed in animal studies despite administration via the oral route. It is assumed in this assessment that 70% of manganese absorbed via the GIT is removed through biliary excretion.

On the other hand, in the case of inhalation exposure, neither absorption control nor elimination mechanisms are as effective in reducing the delivery of toxic concentrations to the target tissues. Deposition and absorption are about an order of magnitude greater after inhalation than after oral exposure. Deposition ranges from about 20 to 60 percent of the amount breathed in, and uptake of the amount deposited averages 70 percent, but can be virtually 100 percent. Intuitively, there seems to be a greater possibility for the direct transfer of manganese from the lungs to the circulatory system and thence to target tissues, after inhalation exposure than after exposure via the GI tract, where chemicals are first routed through the portal vein and the liver after absorption (presystemic clearance or the "first pass" effect). This effect is considered to account for part of the large difference in apparent toxicity between inhaled and ingested manganese. At the same time, it is apparent from the data on tissue retention and clearance that a significant portion of uptake via inhalation, perhaps 60 percent or more, depending on factors such as particle size and intake concentration, goes immediately to the GIT for clearance. As concentrations increase, this mechanism becomes less and less effective in preventing toxic concentrations of manganese from reaching target tissues. It also leaves a significant portion (□40 % ?) of the deposited manganese for distribution directly to target tissues.

It is apparent that the overall clearance of manganese from the body is considerably slower after inhalation exposure than after oral exposure, at least for rodents. This slow clearance opens the possibility of accumulation of manganese in tissues under conditions of chronic exposure, depending on the concentration. The rate of clearance of manganese differs in various tissues, from a few hours in blood to months or even years in the brain. Clearance from the lung itself to tissues and the GIT, while variable due to considerations such as concentration, size and form of particles, appears to be slower than gastrointestinal clearance. Once manganese reaches the brain, there appears to be little difference in clearance time after either intake route. Clearance from the brain is extremely slow from either route. A more important determinant of clearance, as it was of absorption, is the form in which the manganese was presented, for example, soluble or insoluble, valence or oxidation state (Mn^{2+},Mn^{3+}, Mn^{4+}), or size of particle.

Because of the combined effect of all the above factors, it is considered that exposure via inhalation is more likely to lead to toxic concentrations in the target organ, the brain, than exposure via the oral route. However, it is difficult to quantify this difference. Crude calculations estimating absorption and gastrointestinal clearance indicate that perhaps a maximum of 30 to 40 percent of intake via inhalation is available for systemic distribution under normal conditions of exposure, while the corresponding figure for ingestion is 1 to 1.5 percent, or 20 to 40 times lower. Other mechanisms such as slowed clearance and bioaccumulation would act to increase this difference, as would high ambient concentrations.

II.5 Effects of Age

As discussed in section II.1.2, human infants are reported to have about twice as high retention of manganese after 10 days as adults (Mena 1980). A more recent balance study on hospitalized infants found that retention in newborns was virtually complete for both premature and full-term infants. (Zlotkin & Buchanan 1986). This has been well demonstrated in other animal species. Pre-weanling rodents (less than 19 or 20 days old) have much higher absorption and retention than older animals (Mena 1974; Cahill *et al.* 1980; Rehnberg *et al.* 1981; Keen *et al.* 1986). This is due partly to longer retention in the gastrointestinal tract, thus allowing for greater opportunity for gastrointestinal uptake (Rehnberg *et al.* 1985), and partly to immaturity of the liver and biliary excretion system in infants (Miller *et al.* 1975; Mena 1980; Bell *et al.* 1989). These mechanisms will also to some extent affect clearance of inhaled manganese, since at least half is cleared via this pathway. For the purposes of this assessment, it will be assumed that biliary excretion among infants is non-functional.

The blood-brain barrier (BBB) is also undeveloped in the infant, allowing for relatively free ingress of manganese into the brain during this time (to weaning in the rodent). Brain levels attained after dosing with manganese were higher in the infant mouse dosed intraperitoneally at postnatal days 0, 7, or 14 than at day 42, after the development of the blood-brain barrier (Valois & Webster 1989). Manganese in the brain was also cleared much more slowly in the younger animals, and retention at 114 days post-dosing, was 10 times the percentage of administered dose for infant mice dosed at the three earlier ages than for those dosed at postnatal day 42, due to the development of the blood brain barrier, which stopped egress of manganese after it had entered the brains of the younger animals. These effects were independent of concentration, tested at 11 and 25,000 µg/kg body weight. Rehnberg *et al* (1981) also found that the clearance of manganese from the rat brain was slower when Mn was administered beyond postnatal day 18-20. This is the age at which the blood-brain barrier appears to become active, and transferrin-positive receptors are formed in the brain in rats (Connor & Fine 1987).

The elderly may be at increased risk from excessive exposure to manganese, due to increased susceptibility of aging brain cells to injury, added to the "normal" slow loss of neurons as neuron age increases. The dopamine pathways in the basal ganglia are thought to be highly susceptible to age-related neuronal attrition, thus overcoming the considerable functional reserve capacity and leading to long delayed effects (Spencer 1990; Grandjean 1991; Walker & Fishman 1991; WHO 1993a). In one of the few recorded human cases of manganese intoxication via drinking water (Kawamura *et al.* 1941), the severity of the symptoms increased with increasing age, while children were unaffected. Fornstedt *et al* (1990) found that aged guinea pigs (3 years old) had higher levels (219-248%) of dopamine and dopa adducts from autoxidation of catechols than 2 week or 2 month old animals. This indicated greater rate of dopamine autoxication in age than in youth, and may be part of the mechanism underlying loss of dopaminergic neurons in age, since some quinone autoxidation products are cytotoxic. Other neurotoxins which also, like manganese, act on the dopaminergic system have also been shown to exert an age-dependent toxicity on older animals, but not on very young animals. The neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) produced reactive oxygen species and depletion of dopamine in brain striatum of one year old mice, but not in 22 day old mice (David *et al* 1992). The neurotoxin MDMA (3,4-methylenedioxymethamphetamine) caused a drop of 60 to 70 percent in serotonin levels in the frontal cortex and hippocampus of 10, 40 and 70 day old rats, with recovery to control values after 72 hours in 10 day old rats (infant), but not in 40 or 70 day old rats (adolescent or adult) (Broening *et al* 1992).

II.6 Effect of Valence State of Manganese

Both the valence state in which manganese enters the body and its solubility may influence its eventual disposition. After administration by various routes, Mn^{2+} is very rapidly cleared from the blood and efficiently excreted in bile. Gibbons *et al.* (1976) found that Mn^{3+} had a slower elimination rate than Mn^{2+} in cows and pigs; it therefore could have a greater tendency to accumulate in tissues. The oxidation state of manganese may therefore play a key role in differential distribution and accumulation in various tissues, particularly with reference to the brain. Aschner & Aschner (1991) provide a working hypothesis for the differential distribution of the different valence states of manganese: manganese, usually Mn^{2+}, is absorbed from the gastrointestinal tract; in the plasma, a portion is bound to $\square_2$-macroglobulin, is transported to the liver and is excreted via the bile, while a small portion (particularly under conditions of overload) is oxidized via ceruloplasmin to Mn^{3+}, which binds to transferrin in the plasma and is circulated to the tissues including the brain; Mn-transferrin then crosses the blood-brain barrier via an active transfer mechanism, releasing manganese. Inhaled Mn^{3+} would bypass the first steps and be directly bound to transferrin.

Although the metabolism of individual manganese compounds administered by the inhalation route has been examined in several studies, only one study, (Drown *et al.* 1986) has directly compared manganese disposition after administration of two forms, as has been done in several studies of manganese ingestion. Drown *et al.* (1986) administered Mn_3O_4 and $MnCl_2$ intratracheally to mice once only, at a low dose of 200 µg/kg bw. The chloride was cleared from lung four times faster than the oxide, and was mobilized to other tissues faster. Uptake to the brain was rapid, peaking at one day for the soluble chloride and 3 days for the insoluble oxide, with a second peak at 14 days for both. Clearance half-time from the brain appeared to be about 60 to 75 days for the chloride and oxide respectively, with tissue levels still appreciable, but near background, after 90 days. In a study comparing four forms of manganese (chloride, acetate, carbonate (all Mn^{2+}) and oxide (Mn^{4+})) administered in the diet to mice at approximately 200 mg/kg bw/day for 100 days, the manganese content in body tissues increased by 1.5-3 times for all four forms of manganese, varying only slightly between forms, with the only discernable pattern being that manganese content in all tissues was lowest after MnO_2 administration and tended to be highest after administration of the acetate. Food intake was similar for the four forms; body weight gain was similar to controls for manganese carbonate and oxide (insoluble salts), but was reduced for the chloride and acetate (soluble salts). In tests of spontaneous motor activity, the $MnCO_3$ group showed significantly less activity than controls, and some slight reduction was also seen for the manganese acetate group Both Mn^{2+}), while activity was normal for the chloride (Mn^{2+}) and oxide groups (Mn^{4+}) (Komura & Sakamoto 1991). In a second chronic study for 12 months with the same protocol, the effect of various manganese salts on manganese content of liver, kidney and spleen was not as clear as in the 3-month study, possibly because of manganese homeostasis. In blood no differences were seen from controls in manganese levels for all forms except $MnCl_2$ which caused a six-fold increase. In urine, there was a slight non-significant rise in manganese for the manganese acetate and carbonate groups, a six to seven-fold increase for the $MnCl_2$ group, and a 10-fold increase for the MnO_2 group. In seven areas of the brain, the manganese content was variable among forms; manganese content was generally unchanged from controls in corpus striatum, hippocampus, medulla oblongata, and hypothalamus. In the midbrain, manganese tended to decrease, while in the cerebellum, manganese increased, in both cases statistically significantly for the $MnCl_2$ group. Manganese content in the cerebral cortex increased significantly after administration of the insoluble compounds $MnCO_3$ (Mn^{2+}) and MnO_2 (Mn^{4+}), and was also somewhat elevated after manganese chloride and acetate administration. The dopamine and norepinephrine levels of the MnO_2 group (Mn^{4+}) decreased significantly in the corpus striatum and hypothalamus compared with levels in the divalent manganese compound groups or the control. The authors therefore considered that the more highly oxidized compound was more toxic than the three divalent compounds, although they noted that manganese levels in the brain were not related to catechol amine levels. Spontaneous motor activity was slightly depressed in the MnO_2 group (Mn^{4+}) throughout the experiment, and also in the manganese carbonate group (Mn^{2+}). Growth was equally depressed in all groups compared to controls (Komura & Sakamoto 1992). Thus in this series of experiments, in which Mn was administered in the 2+ and 4+ valence state (but not the 3+ state, which may well act more like the more highly oxidized ion), the Mn^{4+} ion (from MnO_2) was inconsistently associated with more deposition in body or brain tissues, or with greater general toxicity.

In a repeat of this experiment (Komura & Sakamoto 1993), gel chromatography studies revealed that more manganese was bound to a higher molecular weight protein (30-80 Kda) in the cytosol of the corpus striatum (49% for $MnCl_2$, 43% for manganese acetate, 33% for MnO_2 and 29% for $MnCO_3$) than in the control group (20%). The authors suggested that this evidence supported the hypothesis that some manganese had been oxidized to Mn^{3+} and was bound to transferrin (m.w. = 75 Kda), the major manganese-binding ligand in plasma (Davidsson *et al.*

1989b). The percent of manganese in the low m.w. fraction (<10 Kda) was lower for MnO_2 (9%) than for the three remaining divalent manganese compounds (36-42%), thus indicating significant differences in binding characteristics between MnO_2 (Mn^{4+}) and the Mn^{2+} compounds for low molecular weight globulins. For the higher-weight proteins believed to be implicated in Mn transfer to the brain, binding took place at 29 to 49 percent, again with the insoluble compounds MnO_2 (Mn^{4+}) and $MnCO_3$ (Mn^{2+}) lower than the two other more soluble manganese salts, both divalent (Komura & Sakamoto 1993). This does not support the hypothesis that a highly oxidized state will invariably be 100% bound to transferrin for entry into the brain, although these authors did not test any Mn^{3+} compound.

Manganese is found in body tissues, including the brain, in both the divalent (Mn^{+2} and trivalent (Mn^{+3}) state (Aschner & Aschner 1991). These authors have reviewed various hypotheses of Mn-induced cellular neurotoxicity, including the following, all except the last relating to the divalent form: mimicry of calcium, Ca^{2+},with substitution reactions or entry through Ca^{2+}-specific channels in membranes; interference with calcium homeostasis; oxidation or autoxidation of dopamine, producing cytotoxic quinones; enhancement of the formation of reactive species, eg. superoxide, and hydroxyl radicals; Mn^{2+}-induced production of 6-OH-dopamine and other toxic quinones and catecholamines (which in turn decrease thiols and attack dopamine); decreased catalase, GSH, and GSH peroxidase levels; and direct toxicity of high valency species, in particular the trivalent form. The latter, including the oxidation of divalent Mn in the brain to the trivalent form has been postulated as a major mechanism for the neurotoxicity of manganese (Archibald & Tyree 1987). These authors succeeded in showing that Mn^{3+}, but not Mn^{2+}, oxidized DOPA (the precursor to dopamine), dopamine, norepinephrine and epinephrine to quinones, and that the Mn^{3+} itself was reduced to $Mn(OH)_2$. All of these compounds have adjacent OH sites, probably the site of action of Mn^{3+}. Other catechol amines without adjacent OH- sites including tyrosine, the precursor of DOPA and dopamine, were unaffected. Mn^{2+} was found to form Mn^{3+} and Mn^{4+} spontaneously at the alkaline pH levels found in the brain. This reaction was thought to be the explanation for the autoxidation of dopamine by Mn^{2+} observed by others. Mn^{4+}, as MnO_2, was also tested, and found to produce a small amount of oxidized dopamine immediately, but the reaction ceased after a few minutes, due to the coating of the MnO_2 particle with unreactive Mn^{2+} precipitate also formed from the MnO_2.

Archibald & Tyree (1987) outlined four mechanisms for Mn^{3+} to be present in the brain: the first was direct uptake of Mn^{3+} from inhalation exposure to the oxides Mn_3O_4 or Mn_2O_3 (this is the major consideration with combustion products from MMT); the second was spontaneous formation of $Mn(OH)_3$, followed by a Mn^{3+}-pyrophosphate chelate, which they showed to be extremely reactive in oxidation of catecholamines; the third and fourth involved oxidation of Mn^{2+} to Mn^{3+} by peroxidases, eg monoamine oxidase, or by reactive oxygen, O_2^-, both known to be found in high concentrations in the substantia nigra. It is concluded from the foregoing that both divalent and trivalent manganese can exert toxicity once they have gained entry to the brain. The divalent form may be toxic in its own right, or may be converted with ease to the trivalent form, which is capable of destruction of the neurotransmitter dopamine.

The other important consideration with regard to effect of valence state is the transport of manganese across the blood-brain barrier, which acts as a major regulator of Mn toxicity to the CNS (Aschner & Aschner 1991). Two mechanisms are involved in the transport of Mn across the blood-brain barrier. The first involves transport of Mn^{2+} across membranes by a saturable mechanism, which is therefore limited in capacity (Aschner & Gannon 1994). The second involves transport of trivalent manganese by an active transport mechanism bound to the high molecular weight protein transferrin, which also binds trivalent iron (Archibald & Tyree 1987; Aschner & Gannon 1994). Manganese is bound to plasma transferrin exclusively as Mn^{3+} (Aisen *et al.* 1969; Davidsson *et al.* 1989a; Aschner & Aschner 1991). Combustion-derived Mn^{3+} in the circulation is immediately available for binding and subsequent transfer, while some of the Mn^{2+} in the plasma is oxidized to the trivalent state by oxidizing agents in the plasma such as ceruloplasmin (Gibbons *et al.* 1976). This conversion in plasma appeared to be time dependent, and took place relatively slowly over a period of up to five days, after which brain concentrations attained levels 13 times higher than baseline levels (Aschner & Gannon 1994). Transferrin binds to a specific cell surface receptor on CNS capillaries, and the complex is then internalized (Aschner & Aschner 1991). Transferrin has also been shown to enter brain endothelial calls by receptor-mediated endocytosis (Fishman *et al* 1985). While the major function of transferrin is the transport of iron, it has been calculated that only 30 percent of the transferrin binding sites would be occupied by Fe^{3+} at normal plasma concentrations, leaving ample opportunity for the binding of Mn^{3+}, which has a similar ionic radius and chelating behaviour to Fe^{3+} (Aschner & Aschner 1991). It is of interest that Mn accumulating areas in the brain, the ventral pallidum, globus pallidus, thalamic nuclei, and substantia nigra, are also Fe-accumulating areas, and are efferent to areas of high transferrin receptor density (Hill *et al* 1985; Aschner & Aschner 1991). Mn-transferrin thus provides a likely hypothesis for transport of trivalent Mn into the brain and delivery to the sites known to be damaged by manganese. Divalent manganese, after transformation to the trivalent form, is also transported by this mechanism.

II.7 Essentiality of Manganese

Manganese is considered to be an essential trace element, and occurs in the cells of all organisms. It is ubiquitous in the body at low concentrations (<200 ppm); tissue concentrations and body content are relatively constant throughout life due to efficient homeostatic control (Aggett and Barclay 1991; WHO 1981). Manganese belongs to the cationic group of essential elements, with zinc, iron, and copper; homeostasis in these elements is effected principally by the gastrointestinal tract and liver. Homeostasis can be overcome by intake of high quantities, by any route including the oral route. Because several protective mechanisms such as control of absorption, biliary excretion, and presystemic clearance act via the GIT, inhalation exposure is more likely than oral exposure to bypass these mechanisms and to result in toxicity.

Manganese is a component of several metalloenzymes; these include pyruvate carboxylase and mitochondrial superoxide dismutase (SOD), which functions in mitochondrial oxygen radical metabolism (Aschner & Aschner 1991). Eighty percent of brain manganese is found in the enzyme glutamine synthetase, which inactivates the excitory amino acid glutamate to glutamine (Wedler *et al* 1984). Manganese also activates a number of enzymes, particularly the glycosyltransferases involved in synthesis of polysaccharides and glycoproteins (Shaw 1980; Szwanek *et al.* 1987). Manganese (Mn^{2+}) and other essential elements were found to prevent death in lethally irradiated mice, and to aid in recovery after administration of non-lethal doses (Sorenson 1992). Metallothionein synthesis was increased 6-fold compared to non-treated mice. SOD-mimetic activity, facilitation of *de novo* synthesis of manganese-dependent SOD, or synthesis of other manganese dependent enzymes was thought to be responsible for this protective action, due to scavenging action on oxygen radicals formed during radiation (Sorenson 1992).

The features of manganese deficiency in experimental animals, namely impaired growth, skeletal abnormalities, depressed reproductive function and ataxia in the newborn, seem to be similar in all animal species studied (Shaw 1980). Skeletal abnormalities in the fetus are thought to be due principally to defective mucopolysaccharide synthesis affecting chondrogenesis. Manganese deficiency in rats induces profound ataxia in the young (Hurley 1968 in Shaw 1980). This is due to disturbed ossification of the otic capsule; provision of manganese on day 14 of pregnancy prevented the defect. This defect can also be genetically determined, and is similarly prevented by administration of manganese (Shaw 1980).

The only reported case of Mn deficiency in humans was in a young man inadvertently given a manganese-free diet in a study; symptoms included mild dermatitis, slight reddening of hair, and depressed vitamin K-dependent clotting factors, unresponsive to vitamin K (Shaw 1980). The natural abundance of manganese in the diet is one explanation for the lack of demonstrated human deficiencies, and it appears also that manganese is essential for humans in smaller amounts than for other mammals.

In order to prevent deficiency syndromes, manganese has been recommended for addition to parenteral nutrition fluids (iv administration), particularly for long-term patients, by the American Medical Association at rates of 0.002 to 0.011 mg/kg bw/day for adults, and 0.002 to 0.01 mg/kg bw/day for paediatric use (Szwanek 1987). Recent observations of manganese deposition in the globus pallidus and basal ganglia of the brain, and accompanying early signs of possible Mn toxicity in nine patients after long-term parenteral nutrition (Mirowitz *et al.* 1991), indicate that these guidelines should be re-examined and possibly lowered.

CHAPTER III. HUMAN HEALTH EFFECTS OF MANGANESE

III.1 Toxicity of Manganese

Exposure to excess manganese has been observed to affect various organ systems, including the respiratory, cardiac, reproductive, and central nervous systems (U.S. EPA 1984). The central nervous system appears to be the critical target organ, with adverse effects observed at lower concentrations than for most other systems, including the reproductive system (Gennart *et al.* 1992). While the lungs may also be a critical target organ for those occupationally exposed to manganese dust, this review will be confined to effects on the central nervous system, which are considered to be potentially more serious than those on the lung, and also more likely to be expressed at lower exposure levels.

The effects of excess manganese on the central nervous system (CNS) have been well documented and reviewed (Mena 1974, 1980; WHO 1981; Barbeau 1984; U.S. EPA 1984; Seth and Chandra 1988). Excess manganese provokes CNS symptomology similar in some respects to the symptoms of Parkinson's disease. Poisoning has been classified as mild, moderate or severe. In the early stages, victims of manganese poisoning show neuropsychiatric symptoms including psychomotor excitement, irritability, lack of concentration, memory deficits, insomnia, anorexia, fatigue, salivation, speech disturbances, hyposexuality, and compulsive behaviour such as irrational laughter, crying, etc. A psychotic period lasting for one to three months, characterized by hallucinations, delusions and compulsions has occurred in some, but not all, cases of manganese poisoning among miners, but does not appear to happen in cases of industrial manganese poisoning. This has been called manganism or "manganic madness" (Mena 1974). Damage is said to be reversible after the first stage of manganese poisoning if the exposure is terminated (WHO 1981; Abbott 1987). Near the end of this period neurological symptoms characteristic of extrapyramidal involvement and disturbances in the basal ganglia occur. These include loss of facial expression (masklike facies), rigidity, bradykinesia (slowness of movement), clumsiness of movement (including an inability to perform repeated movements), impairment of postural reflexes (including retropulsion and walking in the form "pied de coc" with small steps on the toes), speech impairment, tremors, dystonia and muscular hypertonia (Barbeau 1984; Shukla & Singhal 1984; Seth & Chandra 1988). There is a marked interindividual variation in susceptibility to the effects of manganese, with some reports of effects after only a few months of exposure and other after many years. Also, many miners with high tissue levels of manganese do not have the disease while others with apparently normal levels may be affected (Mena 1974; WHO 1981). Obvious signs of manganese poisoning are not usually seen until some time after exposure to 5 or more mg/m^3 Mn in air, but a few subtle signs of manganese toxicity have been observed at considerably lower levels (0.3 to 2.0 mg/m^3) (WHO 1981, 1987; Abbott 1987).

Although the vast majority of cases of manganese poisoning have occurred as a result of exposure to airborne manganese, poisoning is not confined to exposure via inhalation. Animal studies in which large doses were administered in the diet also have demonstrated neurotoxicity. This has only been shown in humans, in two studies (Kawamura *et al.* 1941; Kondakis *et al.* 1989), in which high manganese intake occurred via drinking water (possibly due to a higher absorption of manganese from water than food). In one case report (Ejima *et al.* 1992), parenteral nutrition with excess manganese supplementation (approximately 31 μg/kg bw/d) over 23 months also led to symptoms of manganism/Parkinsonism which were partially reversible after administration of L-DOPA, with manganese deposits evident in the globus pallidus, as shown by MRI. High-density MRI images, traceable to manganese deposits, were also found in the globus pallidus and basal ganglia of the brain in a series of 9 patients (7 females, 2 males) without renal or liver dysfunction, who had been receiving parenteral nutrition supplemented with manganese for an average of 5.3 years (range 5 to 11 y) (Mirowitz *et al.* 1991). A control group of 25 patients not on parenteral nutrition showed no such deposits. Adverse effects, including memory loss, fatigue, weakness, slowing of response time, and inbalance (reported also in several larger epidemiological studies on manganese-exposed workers) were reported by five of the nine patients (mean duration of exposure 6.1 y) in a questionnaire, while responses were negative in 4 patients with a lower average exposure of 4.2 y. The authors suggested that the [American Medical Association] guidelines for dosage of manganese should be re-evaluated.

III.2 Epidemiology

Several epidemiology studies on workers occupationally exposed to considerably lower levels of airborne manganese than miners and others considered above have been completed within the past several years, and are considered here for possible derivation of an ambient objective for airborne manganese.

A cross-sectional study (with certain elements of a cohort study) was carried out by Roels *et al.* (1992) on 92 Belgian workers in a battery factory with exposure to MnO_2 (Mn^{4+}) and matched to a control group of 101 workers from a nearby polymer processing plant. Individual exposures were measured with personal monitors and work histories were used to provide integrated cumulative exposures for each worker. The geometric mean (the distribution was log-normal) for "respirable" dust (particles of 5μm mass median diameter, with a collector cut-off of

7µm, as defined by the British Medical Research Council curve) was 215 µg/m^3, and was 948 µg/m^3 for total manganese dust (particles up to 35-45 µm). Respiratory symptoms, medical histories and neuropsychological complaints and tests were assessed. These data were collected by self-administered questionnaires, spirometric measurements of lung function, clinical measurements (including serum calcium, iron, and the hormones FSH, LH and prolactin, manganese in blood and urine), and by administration of four neurofunctional tests. Other than elevated manganese in urine and blood of exposed workers, none of the clinical or lung function tests were significantly different between manganese exposed workers and controls, and no significant differences were detected in general health complaints (tiredness, weakness etc.). Subtle preclinical signs of neurological dysfunction were detected in three of the four neurofunctional tests administered (no differences were observed in audioverbal short-term memory scores). In three tests of eye-hand coordination (EHC), visual reaction time (VRT) and hand steadiness (HST), manganese-exposed workers were considered abnormal when their test results exceeded the 95th percentile of results in the control group. Eye-hand coordination was significantly worse in 21 /92 Mn-exposed workers (23%) compared to 5/101 (5%) in the non-exposed group. The manganese workers also performed the hand steadiness test and the visual reaction time less satisfactorily than the control workers (12/92 versus 4/101 for hand steadiness, p=0.032, and 7/92 versus 1/101 for visual reaction time, p=0.001 for the last subtest at 6-8 minutes).

Increases in the prevalence of abnormal results were not related to duration of exposure (the average time worked was 5.3 years, or 4.0 years geometric mean) or to current exposure (geometric mean) of 215 µg/m3 respirable manganese dust ($PM_{<7}$) and 948 µg/m3 total manganese dust ($PM_{<35}$). Lack of association with increasing duration of exposure could also be explained by the somewhat limited range of exposure (0.2 to 17.7 years) and by the limited age range of the workers, which reduces the likelihood of a significant duration effect, in view of evidence that older persons are more sensitive than younger persons (see previous discussion).

The prevalence of abnormal results was, however, significantly related to the cumulative measure of exposure (Lifetime Integrated Respiratory Dust or LIRD) which took into account the current average daily concentration and the job history of each employee. The geometric mean LIRD exposure was 793 µg/m^3-years, which is approximately equivalent to 150 µg/m^3 (for an 8-h exposure), when adjusted to a Time Weighted Average basis. (This is the value that was used to represent a LOAEL by the U.S. EPA (IRIS 1993) to derive their Reference Concentration (RfC).)

Some evidence of a dose-response was seen when the cohort was divided into three groups on the basis of cumulative exposure (LIRD) of <600, 600-1200, and >1200 µg/m^3-years. Poorer performance in all three tests was significantly increased in the highest exposure group, and a dose-response trend was evident for hand steadiness (4, 6.5, 12, and 19.4% abnormal responses in the control and three exposure groups respectively), but was less evident for eye-hand co-ordination (5, 21, 27, and 22% abnormal responses). Too few responses (7/92) were recorded to give much confidence in dose-response information for visual reaction time. Since significantly poorer performance in the eye-hand co-ordination tests was seen in all three subgroups, a no-observed adverse-effect level (NOAEL) could not be distinguished on the basis of this analysis (Roels *et al.* 1992).

At the request of the U.S. EPA and others, who hoped to make better use of additional data to give improved dose-response information and to provide an improved approximation of the NOAEL, Dr. Roels made public his data (Roels 1993; see Appendix) for all 92 individual workers, on prevalence of responses, current exposure to respiratory dust, number of years worked, and long-term cumulative exposure (LIRD). [The EPA and commentators undertook a series of reanalyses of these data using various statistical methods, during and after the comment period on the new Reference Concentration which had been established on the basis of this study]

A reanalysis of the results, using the above data and the usual threshold approach as currently applied for guideline- and objective-setting, was also undertaken for this assessment, for the same reasons as above. The exposed population was divided into quartiles of 23 members each; this had the advantage of avoiding the possibility of preselecting the exposure values to demonstrate an effect, but the disadvantage of small numbers in each study group. This technique resulted in demonstration of an improved dose-response for hand steadiness; however, a dose-response for eye-hand coordination was still little evident due to anomalously low responses to the tests in the third quartile of medium-high exposed workers. Results (Table 2) for all three tests were similar to controls in the first quartile, in which the mean (arithmetic average) cumulative respirable manganese dust (LIRD) was 264 μg/m^3-year (range 40-516 μg/m^3-year). The prevalence of abnormal eye-hand coordination was significantly ($p<0.001$) increased in the second quartile (647 μg/m^3-year; range 516-859 μg/m^3-year), and in the fourth (highest) quartile. Significantly poorer performance in hand steadiness was observed in the third and fourth quartiles, and in visual reaction time only in the highest quartile. The No-Observed-Adverse-Effect Level (NOAEL) was considered to be represented by the mean of 264 μg/m^3-year for the first quartile, and the LOAEL by 647 μg/m^3-year, the (arithmetic) average cumulative respirable manganese dust exposures for the two quartiles, based on decrements in eye-hand coordination in the second quartile.

While this analysis did result in some improvement in dose-response information and the possibility of a closer approach to a true NOAEL, it should be pointed out that the power of this analysis to detect a Type II error (accepting the null hypothesis when it is false) is low, due to small sample sizes.

The Roels *et al.* (1992) study itself was in many respects very well carried out. The exposure assessment, often the weakest point in occupational epidemiology studies of this type, appeared to be as well done and thorough as was possible, with individual personal sampling of current exposures and consideration of previous job histories and duration. Respirable particulate matter (PM_7, BMRC defined - see Fig. 10), a more relevant measure with respect to lung penetration and possible health effects than total suspended particulates (TSP or PM_{35}), was measured in addition to TSP. Most important confounding factors (socioeconomic status, hobbies, smoking, personal habits, etc.) were given consideration, and accounted for either in selection of subjects and controls or through analysis of questionnaire responses. Previous occupational history with possible exposure to other metal neurotoxins (lead, mercury, cadmium) was assessed by questionnaire and also by blood and urine sampling, and those with such a history excluded. Educational level was slightly higher in the control group. This could have influenced the results because better scores are expected for the higher educated control group, thus increasing the difference between control and exposed group scores. Such an effect has been shown for at least one of the administered tests (simple visual reaction time) in a validation study (Fittro *et al.* 1992).

A potentially major weakness is the choice of a control group in another nearby factory (although there were 1100 workers in the battery plant). The tests were carried out in both factories, according to the published paper, and were therefore of necessity carried out unblinded for both the investigators and the subjects, who would have been aware of their status. The neurological tests which were given here are much more sensitive than clinical tests, not only to detection of subtle deficits in function (the aim), but also to the attitudes of the administrators of the test and of the persons being tested. Albers (1990) discusses the sensitivity of quantitative sensory and motor testing to "insidious" confounders of motivational factors and the attitudes of those being tested. The unblinded status is therefore a potentially important source of error. On the other hand, the lack of reported neuropsychological symptoms in the exposed group suggests that in fact this type of bias was not a major factor.

A previous cross-sectional study by the same research group (Roels *et al.* 1987a,b) of 141 manganese-exposed workers in a manganese salt and oxide plant. Exposure was to a mixture of oxides including Mn_3O_4, and manganese was present in the Mn^{2+}, Mn^{3+} and Mn^{4+} valence states. Manganese exposed workers performed more poorly, as judged by test results exceeding the 5th or 95th percentile of those in controls, in comparison to 104 control chemical plant workers in the same three tests mentioned above, ($p=0.025$, 0.001 to 0.05, and 0.01 for visual reaction time, eye-hand co-ordination and hand steadiness respectively) and in a fourth test on audio-verbal short-term memory (p= n.s. to 0.01 in various subtests). It is noted that measure-ments of reaction time and scores for the audioverbal short-term memory test for the manganese group were well within the standard deviation for the control group (results for co-ordination and hand steadiness were presented graphically). The incidence of respiratory ailments, particularly acute bronchitis, was increased in the manganese group, as well as increases in some haematological and clinical chemistry values, although spirometric lung function was not altered. Four of 25 subjective symptoms (fatigue, tinnitus, irritability, and trembling of fingers) were significantly increased in the manganese group compared to controls, and a trend toward increases in most other symptoms was also evident. No statistically significant association was found be-tween prevalence of abnormal responses (as defined above) and duration of manganese exposure (average 7.1 years; range >1 to 19 years). The authors suggested several reasons for lack of association with duration of employment: duration did not represent a good estimate of total dose; individual susceptibility was more important; or selection bias (ill workers leaving employment) reduced the number of employee with long service. The latter was suggested by the positive results observed by Siegl and Bergert (1982) in German workers exposed for up to 30 years (mean 16 y) to slightly higher levels of Mn (1100-4000 μg/m^3) (workers were also older in the German study; mean age was 40.1 ±11.2 years, which could also have influenced the findings)

The geometric mean total manganese dust for exposed workers was 940 μg/m^3, virtually the same as in the later study, (range 70 to 8610 μg/m^3), but manganese in blood was 68% higher, indicating higher exposure and/or uptake (Roels *et al.* 1987b). The authors later calculated that the cumulative total average manganese dust exposure was 6700 μg/m^3-year, almost twice as high as the comparable measure of 3500 μg/m^3 in the 1992 study, which could possibly have explained, at least in part, the more pronounced effects noted in this earlier 1987 study. Another explanation could have been the presence of more soluble manganese salts, including sulphate and nitrate, which may have led to increased uptake over the uptake of manganese oxide. [The geometric mean of 949 μg/m^3 was considered as a LOAEL by the U.S. EPA, and became the basis for the former Reference Concentration of 0.4 μg/m^3]. No individual exposure measure-ments were made in this study. Total Mn dust, which includes larger sized particles not considered relevant to lung absorption and potential toxicity, was the only measure given. The authors noted some uncertainty regarding past exposure of the workers, because no monitoring had been done in the past, and considered that it was probably lower than current levels because of exponential increases in production since 1965. Dr. Roels later informed the U.S. EPA that he now thought that this supposition had been incorrect, based on additional information since 1987 (U.S. EPA 1994).

Control of confounding by previous exposure to other neurotoxic metals was done as in the 1992 study, through monitoring and response to a questionnaire on work history. It was necessary to choose the control group from a different factory than the manganese factory, but subjects lived in the same area and were exposed to the same environmental conditions. In this case, care was taken to conduct the study with investigators blinded as to status of those being tested. Tests were carried out at the same location for both subjects and controls, and at the same time each week. A questionnaire on smoking and drinking habits, age, weight, and height, education, socio-economic status, and occupational and health history, enabled these potential confounders to be accounted for. Manganese-exposed workers were significantly younger (mean age 34 y; range 19-59 y) than control workers (mean age 38 y; virtually same range, 19-58 y). This would have had the effect of reducing the differences in scores between exposed and controls, i.e, biasing toward the null hypothesis, since increasing age is known to be correlated to lower scores. This increases the confidence that any differences observed are real. Although the proportion of current smokers was higher in Mn-exposed workers than in controls (67% vs. 48%), the number of current and ex-smokers combined was not significantly different.

The psychomotor tests administered were standardized tests (Roels *et al.* 1982, 1985), and were selected to provide a more sensitive indicator of subtle neurofunctional deficits than the standard clinical tests. The same criticism regarding motivational bias on such tests, made for the later Roels *et al.* 1992 study could be applicable to these results.

A cross-sectional (ecological) study has been carried out on a small group (30 men) of Swedish workers, the 15 men from each factory considered to be the most exposed to manganese, in two steel mills for at least one year. The comparison group was 60 controls in another (manganese-free) steel mill and a mechanical industry (Iregren *et al.* 1990; Wennberg *et al.* 1991, 1992). The mean number of years worked was 9.9 (median 2.6 years) and ranged from a minimum of 1 year to 35 years. The reference group had worked for a mean of 13.4 years. The mean ages were 46.4 and 44.8 for the manganese and reference groups, respectively. Exposure was different in the two manganese-emitting foundries, with means of 180 and 410 $\mu g/m^3$ (overall range 30-1620 $\mu g/m^3$) for total manganese dust (□PM_{35}). The overall mean was 250 $\mu g/m^3$ and the median was 140 $\mu g/m^3$ (Iregren *et al.* 1990) based on area sampling. There were no individual measurements. Respirable manganese dust (not further defined) was estimated to be 20-80% of total manganese dust (approximately 28 and 112 $\mu g/m^3$ based on historical measurements from the 1970s. Conditions were essentially unchanged in the two factories over the past two decades (Wennberg *et al.* 1991, 1992).

Results of a 110-question general medical, occupational and social history questionnaire revealed that the controls had been more exposed to organic solvents than the manganese-exposed cases, but that other factors including smoking habits were similar. Results of a 38-item neuropsychological questionnaire showed higher frequencies reported for tiredness and reduced libido in the manganese exposed group ($p<0.01$). There was also a slight trend (not statistically significant at the 95% level) towards increased respiratory and neuropsychological problems. Four neurophysiological tests were administered; no statistically significant differences were observed in electroencephalograms, event-related auditory evoked potentials, brain-stem auditory evoked potentials or diadochokinesometry (which tests ability for rapidly alternating hand and forearm movement), although poorer performance by the manganese group in all four tests was claimed by the authors. For diadochokinesometry, significance was borderline at p= 0.08-0.12 (Wennberg *et al.* 1991), and was statistically significant at p= 0.02 in the later paper (Wennberg *et al.* 1992).

A test battery from the Swedish Performance Evaluation System, administered by computer, and two manual tests, one for hand dexterity and the other for finger dexterity, were also administered. Poorer performances were noted in the manganese-exposed workers for tests of simple reaction time ($p<0.001$), for finger tapping time ($p<0.05$), and for digit span (p value not given, but only slightly above 0.05). Differences in finger tapping in the non-dominant hand, tapping endurance, additions reaction time, and verbal abilities disappeared after secondary matching, which was found to be necessary for general cognitive abilities, which were higher in one group of controls. There were no differences in hand or finger dexterity, colour word reaction time, or symbol digits (Iregren *et al.* 1990).

In an attempt to test dose-effect relationships, no significant correlations were found between poorer performance effects and total (current) manganese dust measurements or duration of employment. However correlations were reported (Wennberg *et al.* 1991, 1992) between the estimated level of "respirable" manganese dust (value not given) and simple reaction time variability (R=0.47, 9%) as well as digit span (R=0.62, 2%). However, the authors themselves point out that the number of subjects is too small to exclude effects on the outcome from one or two extreme values. Other reasons given for the lack of correlation were small sample size and large differences in susceptibility to effects of manganese exposure. An additional reason may be that few workers had a long duration of service; while the mean was 9 years, the median was only 2.6 years, indicating that only a few workers had many years of service This could be a manifestation of selection bias.

This study did not appear to be as well-conducted as the two Roels *et al.* studies on Belgian manganese workers. As noted above, the numbers of subjects and referents (only 30 after rematching for cognitive abilities) were small for statistical purposes. The workers were chosen to be the most exposed, but no individual measurements were made, and no closer estimate than the current mean and range of exposures from area monitors was made. In addition, little was reported of respirable levels (also not defined as to size) other than the not very helpful observation that they had been 20 to 80 percent of TSP in the past. This is unfortunate, since a correlation was reported between respirable manganese and several of the neuropsychological tests, and also, since smaller ("respirable") particles are more relevant from the point of view of lung uptake and possible resulting toxicity.

The reference group was selected from two different factories, apparently in different geographic locations from the manganese foundries. This could introduce possible differences in environmental conditions, although matching was said to have controlled for this, and Iregren *et al.* (1990) noted that two-way analysis of variance testing did not reveal any differences due to this. In addition, under these circumstances, blinding is not possible for the investigators or the subjects, leaving open the possibility of the "insidious" confounding effect of motivation and attitude discussed above in relation to this type of test in the Roels studies. In the original matching of controls, only age, geographical area and type of work were considered. No consideration was given to socio-economic status, education, or personal habits (smoking, drinking) that could have influenced the comparability of the groups. A secondary matching had to be made to account for greater cognitive ability in the referent group. Matching on education may have avoided this. Neither previous medical histories nor previous work histories and the possibility of exposures (past or present) to other neurotoxicants were considered.

A probable strength of this study is the use of computerized tests for neuropsychological functions (the Swedish Performance Evaluation System or SPES). These types of tests are considered to be less influenced by motivational factors and by the investigators than manual tests or questionnaire responses. More detail could have been provided on how well validated these tests are. The results from this portion of the study are consistent with the findings from the 1987 Roels study, with poorer performance on simple reaction time and memory (digit span) tests. Motor performance tests gave slight differences between this study and the Roels studies, which found adverse effects on eye-hand co-ordination not seen here.

In a recent matched-pair cross-sectional study (Mergler *et al.* 1994) carried out at a ferromanganese and silicomanganese smelter near Montréal, Quebec, 74 workers were paired with 74 referents from the surrounding area who worked at blue-collar jobs unrelated to manganese exposure, or to other chemical industries and processes. Matching was performed for age (± 3 years), educational level, number of children, and area of residence. The mean age of workers was 43.4 y, and of referents 43.2 years. Mean length of residency was 35 and 33 years respectively. The mean number of years worked in the manganese facility was 16.7, and 95% had worked there more than 10 years .

The average (geometric mean) total manganese dust was 225 $\mu g/m^3$, and "respirable" manganese dust, equivalent to PM_{10}, was reported to be 35 $\mu g/m^3$, based on 38 samples from

13 representative areas in the plant. Individual personal sampling results were also taken (Baldwin *et al.* 1991), but were not presented in this analysis [published in Baldwin et al 1993, but not available for this document]. The authors noted that these measurements were likely an underrepresentation of exposure in the recent past, since the smelter was in the process of closing operations and not all jobs were being performed at the time of the survey, one month before closure. Comparison of total manganese measurements of an average group of 14 workers from the furnace area producing silicomanganese (current average exposure 225 µg/m^3) with results from 1989 measurements, also at the time of silicomanganese production, indicated that workers were exposed to twice as much manganese in the past, during production of silicomanganese. Most of the plant's output in the past was, however, ferromanganese; levels of total manganese in 1988 during its production were four times current levels, at an average of 900 µg/m^3 (Baldwin *et al.* 1991). [Dr. Mergler later estimated, in her peer review of the EPA Reference Concentration for manganese, that the geometric mean exposure to respirable manganese particles (PM$_{10}$) in her study was 110 µg/m^3, three times higher than the originally reported value (in comments received from one peer reviewer, October 1994)]

The arithmetic and geometric means of manganese in blood were 1.12 and 1.03 µg/dl respectively for workers, and 0.72 and 0.68 µg/dl respectively for controls; interpair differences were highly significant ($p=0.0001$). This was in the same range as values found in the two Belgian studies (Roels *et al.* 1987a,b, 1992). No differences were observed in urinary manganese, with 0.73 (g.m.) µg/g creatinine for manganese workers and 0.62 µg/g for referents. No explanation was given for the relatively high urinary manganese found in this referent population compared to the range of 0.09-0.17 µg/g observed in referent populations in other studies (Roels *et al.* 1987a,b, 1992; Buchet *et al.* 1993). Both groups lived in the neighbourhood of the smelter, and possibly the high general atmospheric manganese pollution contributed to the high urinary levels of the control population.

In the self-administered questionnaire, few significant differences were observed in sociodemographic characteristics (although more water and less coffee were drunk by the manganese workers), or reported family medical history, but most symptoms considered as pertaining to the central and autonomic nervous system, such as fatigue, nervousness, memory loss, sweating without physical cause, were reported significantly more often by manganese-exposed workers ($p<0.001$ to $p=0.05$ for 19 of 23 symptoms). These results were much more marked than in the Belgian studies or the Swedish study (Wennberg *et al.* 1991), and accord well with what is known of early stages of manganese intoxication. They could be explained by the greater age of this workforce compared to the younger workers in both Roels studies, by the much longer time worked in the smelter (95% longer than 10 years), and by the stability of residence in the environs (many workers for most or all their lives). They could also be explained as bias due to knowledge on the part of the manganese workers who were well aware of their status and of the possible adverse effects of manganese dust exposure. The authors discussed this possibility, and pointed to the fact that only mild symptoms were increased, whereas more serious symptoms would have been reported if the workers were malingering. Several of the 14 neuromotor and musculoskeletal-related symptoms (backache, joint pains, tiredness in the legs) were reported more frequently by manganese workers, but some of these could have been related to the physical exertion required of the job, as the pairs did not seem to be well matched in this regard. Manganese workers reported significantly more difficulty in articulating words than referents ($p<0.01$). Two sensory symptoms, hearing loss and tinnitus, were reported more often by manganese-exposed workers, but these were explained as due to noise damage in the facility rather than manganese exposure.

A wide range of neuropsychological tests, both examiner-administered and computerized (Swedish Performance Evaluation System- SPES) were employed to assess nervous system function. Overall, the manganese workers performed more poorly than the referents on these tests ($p<0.001$). A significantly worse score was noted for the 51-item Motor Scale of the Luria Nebraska Neuropsychological Battery; this was due principally to reduced scores for thumb-finger sequential touch, alternating clench and extension, alternating hand tapping and sequential mouth/tongue movements. Hand steadiness and tremor, as assessed by the Ninehole Steadiness test, was significantly worse in manganese-exposed workers ($p<0.01$ for dominant hand). This result agrees well with results of a similar test in the Roels studies. Differences were not statistically significant for manual or computer-administered tests in simple reaction times, fingertapping speed, two motor dexterity tests (Helsinki/WHO test and Purdue Pegboard test) and grip strength (dynamometer test) The lack of response in the simple reaction time test is surprising in view of the positive results obtained by Roels for a similar test. However, a slowing was noted by the 5th minute of this test, as seen also in the Roels test results. Sensory function test results were similar for both groups, except for increased olfactory acuity in manganese-exposed workers. Speech and cognitive flexibility were measured with various tests; no overall differences were noted for speech (4 tests) while results were significantly better for referents in two of four tests of cognitive flexibility, i.e., the Stroop Colour-Word test and the errors in the Trailmaking B test. No differences were seen in the delayed word recall test, in contrast to the lowered performance for manganese workers noted by Roels in his audio-visual short-term memory test (Roels *et al.* 1992). The average of 110 $\mu g/m^3$ (adjusted from 35 $\mu g/m^3$ based on newer information) respirable dust (PM_{10}) for the single dose group in this study can be taken to represent a LOAEL.

This study presented data from the widest range of tests and questions of any of the four studies, including tests from the Swedish study as well as a number of additional tests. The duration of exposure was also the longest of any of the recent epidemiological studies. The matched-pair design ensured comparability between the exposed and non-exposed groups, particularly with reference to the possibility of confounding by other local environmental pollutants. The major problem with regard to its use in quantitative assessment is lack of reliable and individual exposure data. In addition, the precise physical and chemical nature of the manganese to which the workers were exposed was not given, although this criticism can be applied to all the studies to some degree.

Although there were some differences in types of tests administered and outcomes examined in the various studies, some consistency between the studies is evident with respect to neurophysiological tests showing poorer performance in tasks requiring hand steadiness (all four studies), reaction time, speed and co-ordination, or rapidly alternating hand and arm movements in the Swedish study (Iregren *et al* 1990; Wennberg *et al.* 1991) and the Montréal study (Mergler *et al* 1994). The results thus suggest the first signs of impairment of motor function, consistent also with observations in miners and other manganese workers clinically diagnosed with manganism, and consistent also with damage to the central nervous extrapyramidal motor system noted to result from damage by excess manganese (Barbeau 1984). Reported symptoms, while subject to bias, did appear to correlate to some extent with the degree of exposure and impairment noted in the neurophysiological tests. In the critical study by Roels *et al.* (1992), no significant differences were noted between the two groups with respect to symptoms such as tiredness, loss of libido, irritability, or memory loss, whereas in the previous study by the same group (Roels *et al.* 1987a,b), four of 25 symptoms, including fatigue, trembling fingers and increased irritability, were significantly increased; this group had shown more pronounced decrements on all four of the neurophysiological tests, and their calculated cumulative exposure to total Mn dust was twice as high as the later cohort of workers. In the Swedish cohort (Wennberg *et al.* 1991, 1992), symptoms of fatigue and reduced libido were significant, while all others were not; many of the results in the neurophysiological tests were of borderline significance, and exposure status was difficult to determine. In the Mergler *et al.* (1994) study on Montréal ferromanganese workers, 19 of 23 symptoms, including fatigue, loss of libido, nervousness, and difficulty articulating words, were reported significantly more often in exposed than in unexposed workers in matched-pair comparisons (recall bias due to concerns about possible health effects from working at the smelter was a possibility in this study, but see previous comments). This was also the cohort with the longest exposure to manganese, by a good margin. Since more neurophysiological tests were administered, a larger number of positive results were found in this study than in the other studies, but results for some tests were borderline. The original exposure assessment was known to be an underestimate, and has now been corrected for respirable manganese to three times the original.

A quantitative comparison of manganese exposure of the workers in the four studies is impossible because each of the studies employed different measurements, however a semi-quantitative comparison can be made. In the critical study, several measures were given; for the entire Roels *et al.* (1992) cohort, a measure of cumulative integrated respirable Mn dust equivalent to PM_5, was 793 $\mu g/m^3$-years, calculated to be 150 $\mu g/m^3$ for an annual 8-h shift exposure, and represents a LOAEL for the study. This may be compared to the 110 $\mu g/m^3$ PM_{10} from the Mergler *et al.* (1994) study, and to the average annual value of 70 $\mu g/m^3$ respirable dust estimated from information in Wennberg *et al.* (1991). No such estimate was possible for the earlier Roels *et al.* (1987) study, since respirable manganese dust was not measured or estimated from total dust measurements.

Both duration of exposure and the average age of the exposed populations were increased in the Swedish and Montréal studies over the two Roels studies; average ages were 46 and 43 years respectively (31 and 34 years in the Roels studies), and average duration of exposure was 9.4 and 16.7 years respectively, versus 2.6 (first quartile), 5.3 (overall Roels *et al.* 1992) and 7.1 years (Roels *et al.* 1987a,b). Although duration of exposure *per se* was shown not to be associated with decrements in function, it is connected with increased cumulative exposure, which was shown to be important in the dose-response analysis undertaken on the Roels *et al* study (1992) (see Table II). The Montréal workers, who appeared to be the most affected by exposure to manganese, were also a decade older than the Belgian workers in the Roels studies, and 95% had worked there more than 10 years. The older Swedish cohort sheds no light on this aspect, since it was small, and its exposure was not well characterized.

CHAPTER IV. POTENTIAL AND ESTIMATED MANGANESE EXPOSURE

The exposure of Canadians to manganese will be examined in this chapter from various perspectives. Firstly, temporal, seasonal and geographic trends in ambient monitoring data of respirable manganese will be considered, and comparisons will be made to patterns of MMT usage in Canadian cities. Secondly, a more detailed examination of inhalation exposure to manganese in target cities, including exposure estimates for the upper percentiles of the population, will be carried out and an attempt will be made to translate these into estimates of personal exposure. As a final stage, a multi-media exposure assessment for Canadians of various age groups will be conducted to estimate the fractional contribution of inhalation to total manganese exposure in Canada.

IV.1 Inhalation of Manganese

IV.1.1 Ambient Levels of Respirable Manganese and Relationship to MMT Use

Traditionally, monitoring networks have measured concentrations of total suspended particulates (TSP) in the atmosphere and metal levels associated with those particulates. In order to assess a more biologically relevant particulate measure, agencies have begun monitoring particulate matter of aerodynamic diameter less than 10 µm (PM_{10}), and, in some instances, less than 2.5 µm ($PM_{2.5}$), as well as various elements associated with those respirable particles. The National Air Pollution Surveillance (NAPS) program run by Environment Canada began monitoring respirable particulates in 1984, and now includes 29 sample sites (Dann 1994a). Dichotomous samplers, which divide PM_{10} into the fraction above and below 2.5 µm (the coarse and fine fraction, respectively) are used, as well as size selective inlet (SSI) Hi-Vol samplers. Manganese is measured at a detection level of 0.002 ng/m^3. The Ontario Ministry of the Environment and Energy also maintains an air monitoring network, which currently includes 99 sites (OMEE 1993). Since 1990, the network has included some PM_{10} samplers, the number of which was augmented from 5 to 23 by 1992. These samplers are SSI Hi-Vol samplers, and several associated elements are analyzed for, including manganese.

The trends in respirable (PM_{10} and $PM_{2.5}$) manganese levels in nine Canadian urban centres between 1986 and 1992 as measured by the NAPS program are displayed in Figs. 3 and 4. In most cases, ambient levels of manganese have remained constant, and in some instances levels have declined a small amount. The most notable change is in Montréal, which is apparently due to the closure of a ferro- and silicomanganese plant in Beauharnois, Québec (25 km southwest of

Montréal) early in 1991. The arithmetic mean as well as the standard deviation have decreased substantially, both for PM_{10} manganese and $PM_{2.5}$ manganese. Dann (1994b) estimates that the median PM_{10} manganese for all relevant NAPS sites has decreased significantly at a rate of 3% per year ($P<0.001$) between 1986 and 1992. The mean level of PM_{10} manganese for all samples (1986-1993) is 0.025 ± 0.023 µg/m^3 (Dann 1994a). This would likely be reduced in recent years (1991-1992) due to the substantial reduction in manganese levels in Montréal as a result of the plant closure mentioned above. The monitors in these cities are at elevations between 2 and 17 m above street level.

In order to examine the most recent monitoring data, ambient concentrations of PM_{10} manganese measured in 1992 for various Canadian locations are provided in Fig. 5, both as arithmetic and as geometric means (Dann 1994b; OMEE 1993). Although the focus of this exposure assessment will be on arithmetic mean manganese levels, the comparison of geometric and arithmetic means provides an indication of the frequency of very high exposures. The difference between the arithmetic and geometric means is most pronounced in Hamilton and Sault Ste. Marie, both of which have large steel industries, indicating the occurrence of occasional, very high manganese levels from point sources in those cities.

The lowest value of PM_{10} manganese was measured in Kejimkujic (0.002 µg/m^3), a national park in Nova Scotia which can be assumed to represent a background rural level. Low levels of ambient manganese of 0.011-0.013 µg/m^3 were measured in small cities including St.John, Ottawa and Halifax; moderate levels of 0.015-0.019 µg/m^3 are reported for Winnipeg, Victoria and Calgary; and Vancouver, Toronto, Montréal, Edmonton and Windsor reported higher levels of 0.020-0.025 µg/m^3. These data suggest that in cities without major industrial sources of manganese, PM_{10} manganese is associated with urbanization/city size. The highest concentrations of manganese (0.030-0.158 µg/m^3) were measured in cities with large manganese emitting industries only, with extremely high levels measured by monitors immediately adjacent to the industrial manganese sources (0.100-0.158 µg/m^3). For cities in the NAPS database, $PM_{2.5}$ manganese represents 40-60% of PM_{10} manganese.

Given that ambient respirable manganese levels have remained constant or decreased in Canadian cities between 1986 and 1992, one can examine the concomitant changes in MMT usage as an octane-enhancer in Canadian gasoline. The late 1980's was a critical period in that MMT sales in Canada changed substantially due to the phase-out of leaded gasoline. Specifically, while between 1986 and 1993 national MMT sales by Ethyl Corp. showed a net increase of only 10%, from 1986 to 1989 sales increased 52% and from 1989 to 1993 sales decreased 27% (Wilson, 1994) (Fig. 2). In spite of these shifts, there is no parallel change in respirable ambient manganese in Canadian urban centres, not even in the fine particulate fraction (Figs.3 and 4). (Vehicular manganese emissions are of mass median aerodynamic diameter (MMAD) less than 1 μm, with an average value of 0.4 μm (Ter Haar *et al.* 1975), and are thus expected to contribute more substantially to $PM_{2.5}$).

To examine this more closely, one can examine the *consumption* of MMT in gasoline for a smaller geographical area based on two existing data sets. The Alberta Research Council has conducted annual surveys of the manganese content of all unleaded gasoline grades in the eastern and western regions of the country from 1987-1993 (Alberta Research Council 1987a-1993a, 1988b-1993b). These data are generally based on a limited sample size and may not be statistically representative of the gasoline sold in each region. In addition, the corresponding annual sales of each grade of gasoline for individual provinces are compiled by Statistics Canada (1987-1994). Estimates of manganese sold annually as MMT in gasoline in Québec and Ontario between 1987 and 1993 are presented in Fig 6. (It should be noted that for premium gasoline sales, leaded and unleaded fuel sales cannot be differentiated, and no data are available on the manganese concentration in leaded fuel. From 1987-1990 (when leaded fuel was banned), premium accounted for 15-31% of total fuel sales and regular unleaded accounted for 11-34% of total regular fuel sales, thus premium leaded fuel likely did not account for more than 10% of total fuel sales). Due to a lack of similar data for individual cities, it is assumed that these trends are representative of the urban centres in those provinces. Thus, taking into account gasoline usage, one sees an increase and subsequent decrease in MMT use, similar to the pattern in MMT sales for Canada as reported by Ethyl Corp. (Fig. 2). The decline in MMT usage since 1989 is due to reductions in the manganese content of fuel, as unleaded fuel consumption has increased or remained constant. These changes are not reflected in changes in PM_{10} and $PM_{2.5}$ manganese levels in Quebec and Ontario cities, suggesting that MMT combustion is not a major contributor to those ambient measures.

Manganese concentrations in 1993 Canadian gasoline (regular, medium and premium blends) from across the country (CPPI 1994) are provided in Fig. 1. Separate analyses were performed on summer and winter gasolines. There is no consistent seasonal pattern in terms of gasoline manganese levels: in the western region, the medium and supreme blends have lower concentrations in the summer than in the winter; in Ontario and Québec manganese levels tend to be higher in the summer than in the winter; and in Atlantic Canada regular and medium blends have lower concentrations in the summer and the premium blend has more manganese in the summer. For all regions and grades combined, the average winter and summer concentrations are 8.7 mg Mn/l and 9.1 mg Mn/l, respectively (CPPI 1994). The maximum allowable concentration of MMT in Canadian gasoline is 18 mg Mn/l (CGSB 1986).

There is a significant seasonal difference ($P<0.05$) for $PM_{2.5}$ manganese levels for all NAPS sites between 1986 and 1993 (Dann, 1994b): winter concentrations (median 0.012 $\mu g/m^3$) were greater than summer concentrations (median=0.010 $\mu g/m^3$). Considering individual urban centres (Fig. 7), the data from all cities except Windsor and one monitor in Toronto indicate equivalent or higher $PM_{2.5}$ manganese levels in winter than in summer. Once again, these differences can be compared to seasonal MMT usage patterns for individual provinces (as mentioned above, the necessary data are not available for individual cities). Data of monthly provincial sales of premium, regular and mid-grade gasoline from 1988-1993 are available (Statistics Canada 1987-1993), as well as the summer and winter manganese content of all grades of gasoline for the eastern and western regions of the country from the Alberta Research Council surveys (1987a,b-1993a,b). Combining these data, estimates of manganese sold (and presumably used) in summer (defined as June-August) and winter (defined as December-February) in different regions of the country are presented in Figs. 8 and 9. In Quebec, Ontario, Alberta and British Columbia, more manganese has been sold consistently in gasoline in summer than in winter between 1988 and 1993, due in part to higher manganese levels in some summer fuels and due to increased fuel usage. This is contrary to the air monitoring data and does not support the hypothesis that MMT contributes substantially to fine particulate manganese or to the seasonal variation in fine particulate manganese. The strong seasonal pattern in ambient manganese levels may be driven by meteorological factors such as atmospheric wash-out or humidity.

None of these trends support the U.S. EPA conclusion for the L.A. Basin based on Lyons *et al.* (1993) that 75% of ambient $PM_{2.5}$ manganese is derived from vehicles (U.S. EPA 1994). It is possible that other factors are masking the effect of MMT use, eg. a shift in vehicle miles travelled from urban centres out to rural areas. Data on annual total vehicle miles travelled for large Canadian cities are not generally available. Limited annual data on daily traffic counts for specific intersections (eg. location of ambient monitors) are available, but these counts are often conducted on a single day per year, and the substantial changes in fuel manganese content in recent years would complicate any trends. Thus, it does not seem practical to pursue this issue any further.

IV.1.2 Personal Exposure to Manganese

Ambient monitoring data may not always reflect the actual exposure of individuals living in a given area, because typical human activity patterns result in time spent in microenvironments with higher or lower concentrations of a pollutant and for which we have no monitoring data. Most importantly, it has been estimated that Canadians spend on average 90% of their time indoors, and indoor concentrations of some pollutants can be much higher or much lower than ambient levels. Other microenvironments of importance include, for example, in a vehicle, an urban canyon and an underground parking garage. Hence, a measure of *personal* exposure to a compound is preferable to ambient data, and that estimate should be statistically representative of the population of interest throughout the time period of interest. Several studies in recent years have assessed personal inhalation exposure of groups of individuals to manganese, and these are reviewed here. It should be noted that in most of these studies only a small sample size of individuals and a narrow temporal window were monitored.

The 24-hour average personal exposure of Toronto office workers (selected in a nonstatistically representative manner but intended to be indicative of general population exposure) and cab drivers (selected as a high-exposure sub-population) to manganese was assessed by Lynam *et al.* (1994) in February 1991. Manganese was measured in total suspended particulates rather than in a respirable form. Mean 24-hour exposure for office workers and cab drivers was 0.013 ± 0.009 μg Mn/m^3 and 0.035 ± 0.010 μg Mn/m^3, respectively. Based on ambient monitoring data available for Toronto for February 1991 (Radell 1994), the arithmetic mean level of manganese in TSP measured at five sites was 0.042 $\mu g/m^3$. These levels are comparable to the 24-hour personal exposure of taxi drivers, and are considerably higher (three fold) than the personal exposure of office workers, possibly indicating the importance of low indoor manganese levels to total human exposure. This suggests that personal exposure to PM_{10} manganese would also be lower than levels measured by ambient monitors, for the general Canadian population.

Subsequently, Zayed *et al.* (1994a) assessed at-work and off-work manganese exposure of two potentially at-risk groups in Montréal: taxi drivers and garage mechanics. Data were collected in June 1992 and again, manganese in total suspended particulates was reported. Mean manganese concentrations in the workplace of taxi drivers and mechanics were 0.024 μg Mn/m^3 and 0.250 μg Mn/m^3, respectively, both of which were significantly higher than the off-work levels of 0.007 $\mu g/m^3$ and 0.011 $\mu g/m^3$ measured for the two groups, respectively. 24-hour average exposures for a seven day week are estimated at 0.012 μg Mn/m^3 and 0.085 μg Mn/m^3 for taxi drivers and garage mechanics, respectively (assuming 10 m^3/day air intake at work (ICRP 1975) and a 5-day work week). It was noted by the authors that the garage mechanics, all ten of whom worked in the same garage, did not always vent the vehicle exhaust to the outdoors as is appropriate. This is supported by the fact that the manganese level in the garage when the doors were closed was double the level when the doors were open (0.31 $\mu g/m^3$ vs. 0.152 $\mu g/m^3$). TSP manganese concentrations in Montréal in June, 1992 were measured by the Communauté urbaine de Montréal (Gagnon 1994) at 10 sites: the mean value for the city was 0.04 $\mu g/m^3$. This is substantially higher than the 24-hour exposure of taxi drivers estimated by Zayed *et al.* (1994a), but less than that of the garage mechanics. 24-hour average exposure for the garage mechanics is estimated to be 0.054 µg Mn/m^3 based on at-work exposure of 0.15 µg/m^3 as was measured under adequate ventilation conditions, which is still somewhat higher than the ambient level.

Zayed *et al.* (1994b) recently (January 1994) assessed the personal manganese exposure of office workers and taxi drivers in Toronto and Montréal including both total and respirable cut-off points of manganese, the latter intended to be directly comparable to the sampling methods used by Roels *et al.* (1992) which measures a fraction somewhat smaller than PM_{10} (Fig. 10). 24-hour average exposures of office workers in Toronto and Montréal to respirable manganese were 0.010 ± 0.008 µg Mn/m^3 and 0.002 ± 0.001 µg Mn/m ,^{3}respectively. Similar exposure measures for cab drivers in Toronto and Montréal were 0.014 ± 0.008 µg Mn/m^3 and 0.006 ± 0.006 µg Mn/m^3, respectively. Thus, vehicle-related activities appear to contribute to manganese inhalation exposure in our cities. For office workers, respirable manganese was 90% and 65% of TSP manganese in Toronto and Montréal, respectively. Among cab drivers, respirable manganese represented 54% and 78% of total manganese exposure in those cities. Unfortunately, only limited ambient monitoring data are available for that period for comparison: in Montréal PM_{10} manganese (at a single monitor) was <0.010 µg/m^3 (Gagnon 1994). As mentioned above, *respirable* in the Zayed *et al.* (1994b) study is defined at a somewhat lower value than PM_{10}, but the personal exposure in Montréal is comparable to the ambient PM_{10} value.

Manganese in total suspended particulates was measured both indoors and outdoors of volunteer's homes and offices during summer 1991 and winter 1992 as part of the Windsor Air Quality Study (Bell *et al.* 1994). Arithmetic mean indoor concentrations of 0.005 µg Mn/m^3 and 0.007 µg Mn/m^3 were measured in homes and offices, respectively. The concomitant mean outdoor concentration was 0.018 µg Mn/m^3. Given the time reported spent at home, in the office and outdoors (including commuting) of participants (14.5 hours, 6.6 hours, and 2.9 hours, respectively) the mean 24-hour exposure level was 0.007 µg Mn/m^3. During the summer months, indoor levels ranged from 0.004-0.012 µg Mn/m^3 and outdoor levels from 0.016-0.038 µg Mn/m^3 for different areas of Windsor. These data underline the fact that indoor TSP manganese concentrations are lower than outdoor levels, and thus possibly explain why average personal exposure measures appear to be less than ambient monitoring levels.

Egyed and Chan (1994) measured respirable manganese as PM_5 in vehicles during rush-hour in Toronto in February and March, 1994. The mean level of manganese in all vehicles was 0.045 µg/m^3 ± 0.017 µg/m^3. This likely indicates elevated levels of manganese exposure associated with high traffic in an urban area. No comparable ambient monitoring data are yet available for that time. Loranger *et al.* (1994a) report significantly ($P<0.05$) higher levels of TSP manganese in high traffic areas compared to low traffic areas in Montréal. As part of the *Outdoor*

Air Quality in Toronto study, the Toronto Department of Public Health (1993) measured TSP manganese for a two day period in both March and June, 1990 at nose-level (1.5 m) at three Toronto sites characterized by low, medium and high traffic volumes. The respective manganese measures at these sites were 0.028 μg/m^3, 0.044 μg/m^3 and 0.053 μg/m^3, clearly indicating an increasing trend with increasing traffic volume.

The most comprehensive personal exposure monitoring data available for manganese is provided by the Particle Total Exposure Assessment Methodology (PTEAM) Study conducted by Clayton *et al.* (1993). 178 participants, statistically selected to represent 139 000 residents of Riverside, California were assessed for personal inhalation exposure (PEM) to PM_{10} manganese from 7 AM to 7 PM, and 7 PM to 7 AM. All data were collected over a two month period in the fall of 1990, and thus may not be representative of year-round exposure. All individuals were non-smokers over the age of ten years. Arithmetic mean personal exposures of 0.069 ± 0.065 μg Mn/m^3 and 0.024 ± 0.017 μg Mn/m^3 were reported for the daytime and nighttime, respectively. Indoor and outdoor stationary monitors collected data of PM_{10} manganese simultaneously to the personal exposure monitoring, and the corresponding daytime and nighttime means from the outdoor samples were 0.051 and 0.037 μg Mn/m^3, and from the indoor samples were 0.038 and 0.022 μg/m^3 (Pellizzari *et al.* 1993). The outdoor and indoor monitors (but not the personal exposure monitors) also measured $PM_{2.5}$ manganese: daytime and nighttime average $PM_{2.5}$ manganese concentrations were 0.012 and 0.010 μg/m^3, respectively, for outdoor samples, and 0.010 and 0.008 μg/m^3, respectively, for indoor samples.

Published data from the PTEAM study all address nighttime and daytime exposures separately: for comparison to Canadian ambient monitoring data, 24-hour averages are more appropriate. To this end, the original data were obtained from the PTEAM project lead, Lance Wallace (1994). Based on these data, the 24-hour PEM arithmetic mean is 0.045 μg Mn/m^3 and the outdoor arithmetic mean is also 0.045 μg Mn/m^3, and thus the ratio of PEM:outdoor ambient values is 1.0. For the PEM data, the 90th and 99th percentiles of 24-hour exposure were 0.082 and 0.212 μg/m^3: based on outdoor monitoring data, the 90th and 99th percentiles of 24-hour exposure were 0.068 and 0.129 μg/m^3.

Several conclusions can be drawn from the data. Personal exposure is underestimated by outdoor stationary monitoring devices during the daytime hours during which an individual may have many microenvironment-related activities. The reverse is true at night, during which personal exposure is lower than ambient measures. If one considers mean 24-hour population exposure to PM_{10} manganese, estimates based on personal exposure monitoring (PEM) are equal to those from stationary monitors, and the 90th and 99th percentiles of the PEM data are 1.8 and 4.7 times higher than the arithmetic mean from the outdoor stationary monitors, respectively (Table 3). The ratio of manganese exposure as measured by PEM to that measured by stationary ambient monitors for various population percentiles from the PTEAM study are shown in Fig. 11: it is evident that for the 75th percentile and less, ambient monitors overestimate personal exposure while for the upper 25% of the population the reverse is true. This suggests that a segment of the population receives high exposure to particulates at some point during their day (eg. standing at a bus stop, vacuuming), which is not reflected in the data measured by stationary ambient monitoring devices at the individual's home. It is not clear whether or not personal exposure would be better characterized by an ambient monitor in a downtown location. In addition, PM_{10} manganese levels measured by stationary monitors inside a house are consistently lower than concentrations measured by stationary samplers outside a house for all percentiles of exposure for both PM_{10} and $PM_{2.5}$.

The data *per se* cannot be assumed to be representative of Canadian exposure, as the outdoor PM_{10} value (0.045 $\mu g/m^3$) is approximately twice the level measured in recent years in major Canadian cities without manganese emitting industries. Compared to the personal exposure respirable manganese data collected in Canada (Zayed *et al.* 1994b), the 24-hour mean personal exposures are 4 to 20 times higher in Riverside. In addition, manganese sources and particle size distribution may be very different in Canadian urban centres, as MMT is in limited use in the U.S. (in leaded fuel only), and thus industrial and/or crustal sources are possibly more important in Riverside. In their MMT exposure assessment, the U.S. EPA (1994) based estimates of personal manganese exposure on the assumption that 75% of ambient $PM_{2.5}$ manganese is derived form MMT combustion. Given the lack of correlation between MMT usage and ambient $PM_{2.5}$ manganese levels in Canadian cities (see section IV.1.1), this assumption does not appear to be valid in Canadian cities. In addition, the population distribution of exposure may be different depending on the manganese sources and human time activity patterns, the latter of which may be quite different for the Canadian situation.

In summary, the use of personal exposure data is preferable to ambient monitoring data if the PEM data are a valid representation of exposure for the population of interest. The results of the studies reviewed above are displayed in Fig. 12. The Canadian personal exposure monitoring studies may not be robust in terms of sample size, time frame, or statistical representativeness, yet the repeated measures of relatively low exposure to manganese in our largest cities lend weight to the findings. The results suggest that 24-hour personal exposure to manganese in Canadian cities is overestimated by ambient monitoring data for the general population, and also for a presumably highly exposed sub-population, i.e. taxi drivers. Garage mechanics are the only group studied which showed personal exposure above average ambient levels, a situation that was substantially ameliorated when the garages were adequately ventilated. Personal exposure for the upper quartile of the population may be higher than outdoor ambient manganese as measured immediately outside the home: whether or not the upper percentiles of personal manganese exposure are underestimated by ambient monitoring data collected in a high traffic area of a downtown core remains to be determined. Respirable manganese in the indoor environment is generally less than the level outdoors

IV.1.3 Canadian Inhalation Exposure to Manganese

Although MMT-derived manganese emissions are within the fine particulate fraction, PM_{10} rather than $PM_{2.5}$ manganese was chosen as the relevant parameter for this exposure assessment as the pulmonary region is exposed to particles up to 10 µm in diameter (EPA 1982). In addition, in section Chapter V of this document, a reference level (C_{air}) of manganese will be derived based on the epidemiological study of Roels *et al.* (1992). In that study, respirable dust/particulate was defined according to the method of the British Medical Research Council (BMRC): 0% penetration to the alveolar region for particles □ 7.1 µm in diameter, and increasing penetration for smaller particles with up to 100% penetration for particles □ 0.5 µm (Fig. 10) (ACGIH 1971). As ambient monitoring devices do not measure the BMRC-defined respirable fraction and as it is not possible to translate PM_{10} data to a value equivalent to the BMRC measure, PM_{10} data will be used in this exposure assessment. This is a conservative estimate of exposure, as the BMRC-defined particulate measure and the Health Canada derived C_{air} are a fraction of PM_{10}. Only PM_{10} manganese will be discussed in the following sections.

This exposure assessment has been conducted for two sets of air data. Firstly, as mentioned above, the most recent available data (1992) from outdoor stationary ambient monitors have been used, and the primary estimates of exposure have been based on these data. Secondly, an attempt has been made to translate these values to population estimates of personal exposure based on the findings of the PTEAM study, inspite of the above-mentioned uncertainties in extrapolating the results from Riverside, California to Canadian urban areas. The PTEAM results have been used because of the large sample size, the resulting population distribution of exposure, and the concomitant collection of PM_{10} manganese by stationary samplers outside an individual's home and by personal exposure monitoring. Based on the 24-hour PTEAM data, the ratios of 24-hour PEM PM_{10} manganese measures for different percentiles of the population to the arithmetic mean value measured by stationary outdoor monitors are provided in Table 3. From these data, the ratios of the arithmetic mean, 90th and 99th percentiles of the PEM data to the outdoor arithmetic mean (1.0, 1.8 and 4.7, respectively) have been extracted. These ratios have been used to convert the annual ambient PM_{10} manganese means for Canadian cities to estimates of the mean, 90th percentile and 99th percentile of personal exposure for populations in those Canadian urban centres.

Because the available data indicate that indoor air levels of manganese are less than outdoor levels (see section IV.1.2) and because respirable manganese levels in Canadian indoor environments are poorly characterized, this exposure assessment will assume 24 hour exposure to outdoor ambient levels. The estimates of personal exposure should incorporate differences from ambient exposure due to personal activities. Although it would be preferable to distinguish between daytime and nighttime ventilation rates and exposure, the Canadian ambient monitoring data for respirable manganese are collected as a 24-hour average only. Data from the monitor recording the highest levels of respirable manganese in a given city have been used, in order to characterize exposure of individuals living in the more highly polluted areas. Thus, the following exposure assessment is based on several conservative assumptions.

In the following exposure assessment, unless otherwise stated, the use of *mean* refers to the *arithmetic mean*.

IV.1.3.1 Selection of Canadian Cities

In order to examine manganese inhalation exposure for the general Canadian population, several urban areas were selected. These were of three types: i) a small city with moderate vehicular traffic and no major industrial manganese sources; ii) a large city with high vehicular traffic and no major industrial manganese sources; and iii) a city with identifiable manganese-emitting industries.

The most recent (1992) annual PM_{10} manganese data collected by the Environment Canada NAPS network and the Ontario Ministry of the Environment and Energy network have been used. Data from 1992 were selected because they are the most recent available, because the manganese levels in Montréal prior to 1991 were influenced by emissions from a nearby industry in Beauharnois, and because the OMOEE monitoring network has been monitoring PM_{10} manganese since 1990 only, and the number of monitoring stations increased drastically from 5 to 23 from 1990 to 1992.

The annual (1992) mean PM_{10} manganese data for Saint John (New Brunswick), Walpole Island (Ontario), Halifax (Nova Scotia) and Ottawa (Ontario) were the lowest in the NAPS database (0.011-0.013 µg Mn/m^3). Saint John (NAPS station #40203 @ 0.011 µg Mn/m^3 and @ 5m elevation above street level) was selected as the type one city. Montréal, Toronto and Vancouver had relatively high levels of PM_{10} manganese (0.015-0.025 µg Mn/m^3), and Montréal was selected as the type two city as the annual mean (NAPS station #50109 @ Duncan/Décarie @ 4m elevation) was the highest (0.025 µg Mn/m^3). Although sampling in a given city is limited and therefore even the highest monitored levels may underestimate the worst case scenario, the highest measured values were used in order to be conservative in our exposure estimates. The NAPS station in Montréal used for the assessment is located close to the intersection of the Décarie Expressway and the Métropolitain Autoroute, a highly trafficked location and thus considered appropriate as a worst case area for Montréal.

Finally, two cities with large manganese emitting industries and high levels of ambient manganese were selected: Hamilton and Sault Ste. Marie, Ontario. PM_{10} manganese data for 1992 were available for these cities from the Ontario Ministry of the Environment and Energy. Data for the monitoring stations with the highest manganese measures were selected as the most conservative estimate of exposure available: Hamilton (OMOEE station # 29313 @ Gertrude/ Depew @ 4m) had an annual mean of 0.100 μg Mn/m^3; and Sault Ste. Marie (OMOEE station # 71342 @ Bonney St. @ 2m) had an annual mean of 0.158 μg Mn/m^3. Although these sites are located close to industrial centres, they are adjacent to residential areas. The purpose of including industrial towns is to examine the most severe Canadian ambient exposure to manganese (albeit unrelated to MMT use), and to determine whether or not there is a health risk.

IV.1.3.2 Manganese Exposure Based on Ambient Monitoring Data

Ambient levels of PM_{10} manganese (1992) for the four targeted urban areas are presented in Table 4, along with the 90th and 99th percentiles of values measured at those sites. These percentiles represent temporal extremes (the percentage of times per year that concentrations above a given level have been measured at that site) and *not* spatial variation (i.e. the percentage of areas or population with concentrations above a given level). However, for lack of better data, it will be assumed that these percentiles approximate the percentage of the population exposed to those concentrations of PM_{10} manganese. It is clear that the concentrations in the two industrial cities are much higher than those in non-industrial urban centres, and that the ratios of the 90th and 99th percentiles to the mean are also much higher in the industrial areas. This suggests that infrequent but very high concentrations occur in association with industrial manganese emissions, and less so in urban areas without manganese-emitting industries.

The mean levels of ambient manganese in St. John and Montréal are 0.011 μg/m^3 and 0.025 μg/m^3, the 90th percentiles are 0.021 μg/m^3 and 0.034 μg/m^3, and the 99th percentiles are 0.024 μg/m^3 and 0.041 μg/m^3, respectively. Conversely, the mean ambient concentration in Hamilton and Sault Ste. Marie are 0.100 and 0.158 μg/m^3, while the 90th percentiles are 2-3 times higher and the 99th percentiles are 4-5 times higher.

As discussed in section II.1.1, it has been assumed for this assessment that 60% of PM_{10} manganese is deposited in the lung and that 100% of this is available for uptake into the circulatory system. Inhalation exposure to manganese for different age groups in the population based on ambient monitoring data is presented in Table 5. Manganese uptake in St. John and Montréal, including the upper percentiles, is less than 0.6 µg/day or 0.011 µg/kg bw/day for all age groups, with average uptake ranging from 0.002-0.007 µg/kg bw/day. For the 90th and 99th percentiles of exposure uptake ranges from 0.004-0.009 µg/kg bw/day and 0.004-0.011 µg/kg bw/day, respectively. Average manganese inhalation uptake is markedly higher in Hamilton and Sault Ste. Marie at 0.017-0.042 µg/kg bw/day, and the 99th percentile of exposure is up to 0.22 µg/kg bw/day. On a body weight basis, uptake peaks in the 5-11 year age category, but does not vary greatly between age groups.

IV.1.3.3 Manganese Exposure Based on Estimates of Personal Exposure

The Canadian ambient mean PM_{10} manganese data have been converted to estimates of population personal exposure based on extrapolations from the PTEAM study. As described in section IV.1.3, the ratios of the 24-hour arithmetic mean, 90th and 99th population percentiles of the PEM data to the ambient mean were 1.0, 1.8 and 4.7, respectively. Assuming a similar distribution around the Canadian means, these ratios have been used to estimate the mean, 90th and 99th percentiles of personal exposure in Canadian cities from the Canadian ambient means provided in Table 4. Again, there is considerable uncertainty in this extrapolation to any Canadian city, however, these estimates provide an indication of potentially high exposures in the upper percentiles of the population living in the vicinity of the ambient monitors. The estimates are presented in Table 6, in which mean exposures are obviously identical to those based on the ambient monitoring data. Considering St.John and Montréal, the 90th percentiles of exposure are 0.020 µg/m^3 and 0.046 µg/m^3, respectively, and the corresponding 99th percentiles are 0.052 µg/m^3 and 0.118 µg/m^3. The exposure of the 98th percentile in Montréal is 0.080 µg Mn/m^3, and the elevated estimate for the 99th percentile is due to two individuals' personal exposure in Riverside, California. The 90th percentiles of exposure in Hamilton and Sault Ste. Marie are 0.183 µg/m^3 and 0.289 µg/m^3, respectively, and the 99th percentiles range from approximately 0.45-0.75 µg/m^3.

Considering manganese uptake (Tables 5 and 7), estimates based on personal exposure data indicate that although the population means are the same as those based on ambient monitoring data, the 99th percentiles of personal exposure in St. John and Montréal are much higher than those based on ambient levels. The 90th percentiles based on ambient data and PEM estimates are similar in St. John, but the latter are approximately 30% higher in Montréal. However, the 90th and 99th percentiles of personal exposure in Hamilton and Sault Ste. Marie are lower than those based on ambient monitors, with the exception of the 99th percentile in Hamilton, which is 30% greater for personal exposure.

Considering inhalation uptake for different age categories, the 90th percentiles in St. John and Montréal range from 0.003-0.012 µg/kg bw/day, and a maximum value of 0.032 µg/kg bw/day is estimated for the 99th percentile. For the industrial cities, the 90th percentile of inhalation uptake ranges from 0.031-0.077 µg/kg bw/day, while the 99th percentile is as high as 0.2 µg/kg bw/day among 5-11 year olds in Sault Ste. Marie. As in the estimates based on ambient data, manganese inhalation uptake peaks among 5-11 year olds.

IV.2 Ingestion of Manganese

IV.2.1 Dietary Manganese

The primary source of manganese exposure is generally attributed to oral exposure due to the natural content of manganese in the diet (Mena 1981). Estimates of mean dietary intake of manganese reported worldwide are presented in Table 8. The U.S. Food and Nutrition Board recommends an adult daily intake of 2.5 - 5.0 mg Mn/day (NRC 1989). The Canadian studies listed in Table 8 indicate that adult manganese intakes from ingestion are in fact in that range.

Because of the lack of a recent and comprehensive survey of Canadian dietary manganese, estimates of the daily manganese oral intakes of Canadians were calculated for this exposure assessment based on existing data on food consumption and manganese levels in foods. Specifically, Canadian daily consumption of individual food groups were based on CEPA estimates for different age categories (Health Canada 1994), and the manganese content of individual foodstuffs was obtained from the Canadian Nutrient File, which is maintained by the Bureau of Nutritional Sciences of the Foods Directorate of Health Canada. Data in the Canadian Nutrient File are based on available Canadian data as well as on data published in the U.S. Department of Agriculture Handbook # 8, 1979 - 1993 (Br□lé, 1994). In cases where several values were provided for subgroups of the food group (eg. salt water fish species, ready-to-serve soups), a composite mean of the available data was calculated. Unfortunately, data were lacking for several of the cereal and grain products, noted in previous studies as one of the major sources of dietary manganese (Méranger and Smith, 1972; Lewis and Buss, 1988). In those cases, data from the U.S. Total Diet Study (Pennington and Young, 1990) were used as a surrogate.

For infants aged 0 to 6 months, four different approaches were taken. As mentioned above, estimates of manganese consumption based on the Canadian Nutrient File data were made. In addition, estimates of manganese intake were made for infants who consume exclusively breast milk, milk-based formulas or soya-based formulas. In all three cases, it was assumed that infants consume 0.75 kg/day (Health Canada, 1994). Mean concentrations of manganese in Canadian milk-based and soy-based ready-to-use formulas were 0.010 mg/100g and 0.063 mg/100 g, respectively (Dabeka and McKenzie, 1992). The manganese content of human milk is substantially lower: an American study reported a value of 0.002 mg/100g (Vaughan *et al.* 1979).

The manganese content of different food groups, consumption patterns, and the contribution of each foodgroup to total dietary intake of manganese are provided in Table 9. Principal sources of dietary manganese include cereal and grain products, derived predominantly from breads and wheat flour (38.1 - 53.8 %), and tea (22.0% for adults). Other sources include vegetables (such as peas and potatoes), fruits and wine, while dairy products, meat products and fish/shellfish combined contribute less than 4% of daily manganese for any age group.

Estimates of total dietary intakes of manganese for all age categories, including four estimates for infants, are provided in Table 10. In the case of infants, daily manganese intake varies greatly with diet (0.015 - 0.66 mg/day), with breast-fed infants consuming the least manganese and those fed "adult" foods consuming the most. Vuori (1979) found similarly low levels (0.003 - 0.004 mg/day) of daily manganese intake among breast-fed infants one to three months old in Finland. Previous Canadian estimates of infant dietary manganese (Kirkpatrick *et al.* 1980) ranged from 0.47 to 1.04 mg/day depending on the age of the children (0 - 6 months), which are at or above the estimates presented here. This may be due to societal changes in infant diets.

The intake estimate for children 7 months to 4 years old (1.7 mg/day) is similar to that reported by Gibson *et al.* (1985b) for 22 month old Canadian children (1.5 mg/day). Estimates of dietary manganese are generally higher than those reported for the U.S. (Pennington *et al.* 1989) and lower than those reported for Australia (Fardy *et al.* 1992) (Table 8). The estimate of adult intake (3.53 mg/day) is similar to those previously reported for the Canadian population (Drolet and Zayed, 1994; Gibson and Scythes, 1982; Gibson *et al.* 1985a; Kirkpatrick and Coffin, 1977; Méranger and Smith, 1972) and falls midway in the range of the U.S. recommendation of 2.5 - 5.0 mg/day (NRC, 1989). In a study of manganese retention in adult males, Freeland-Graves *et al.* (1988) estimated a dietary intake of 3.5 mg/day to be necessary in order to maintain a positive manganese balance.

IV.2.2 Manganese in Drinking Water

Comprehensive surveys of Canadian drinking water quality have not measured manganese. A drinking water guideline of □ 50 µg Mn/l as an aesthetic objective is recommended by Health Canada (1993), and a health-based guideline of 500 µg Mn/l has been recommended by WHO (1993b). Several provincial and municipal governments have monitored manganese levels in drinking water. In general, the concentration of manganese in surface waters is lower than that in groundwater, due to the more acidic and reducing conditions in subsurface waters which facilitate the dissolution of manganese oxides (U.S. EPA 1984).

Data on manganese levels in drinking water have been obtained for Montréal (Environment Québec), St. John (New Brunswick Department of Health and Community Services), Hamilton and Sault Ste. Marie (Ontario Ministry of the Environment and Energy). The city of St. John relies on both surface and groundwater, and annual mean manganese levels (1990) reported for central locations range from <5-19 µg Mn/l (Ecobichon and Allen 1990). Mean levels of manganese in the drinking water of municipalities on the island of Montréal measured between 1977 and 1993, range from <10-64 µg Mn/l, except for a single sample in Lachine in 1983 that measured 470 µg Mn/l. These municipalities rely exclusively on surface water sources. It should be noted that most of the Montréal samples were collected prior to 1985, after which time Québec Environment limited their monitoring to substances covered by the Reglement Sur L'Eau Potable (M.E.F., 1993).

The city of Hamilton also relies on surface water as a drinking water source, and a maximum level of 4 µg Mn/l was measured between 1988 and 1993 in distributed and flowing tapwater (mean = 1.8 µg Mn/l). Conversely, Sault Ste. Marie makes use of both surface water and groundwater from four municipal wells, and somewhat higher levels were detected for the same time period (1988-1993): a maximum level of 19 µg Mn/l was measured in distributed and flowing tapwater, and the mean level was 7.8 µg Mn/l (OME 1990b,c, 1991a,b, 1992b,c; OMEE, 1994a,b).

Thus, for all four cities of interest in this exposure assessment, the concentrations of manganese in drinking water are generally below the aesthetic guideline of 50 µg Mn/l, and, with one exception, are well below 100 µg Mn/l. According to ATSDR (1991), national U.S. surveys of drinking water manganese have reported that 95% of samples in 100 American urban centres contain less than 100 µg Mn/l. Therefore, for the purposes of this exposure assessment, a conservative assumption of a maximum concentration of 100 µg Mn/l in drinking water has been made for all four locations.

IV.2.3 Soil Manganese

Manganese is very abundant in the Earth's crust, and occurs at relatively high and variable concentrations in Canadian soils. In a review of the literature, McKeague *et al.* (1979) reported Canadian soil manganese concentrations ranging from 54 to 5740 µg/g. The authors completed a comprehensive survey of background manganese levels in soils from five major geological areas of Canada, and reported a national mean concentration of 520 µg/g (range 69-4295 µg/g). The means for the five regions ranged from 378-787 µg/g (McKeague and Wolynetz, 1980). Studies of urban soils have reported similar levels for total soil manganese: 281-467 µg/g for Montréal soils, the higher values associated with sandy rather than organic soils (Brault *et al.* 1994); 522 µg/g in Montréal soils with either high or low exposure to manganese derived from MMT (Forget *et al.* 1994); and 474-685 µg/g for street dust samples in Halifax (Fergusson and Ryan 1984). Vermette *et al.* (1987) reported a much higher mean concentration of 2519 µg Mn/g in street sediments from Hamilton, a city with large manganese-emitting industries. A spatial distribution of soil manganese in the Hamilton area indicated the highest levels nearest to the industrial centres.

Because of the minimal sample sizes in the Montréal and Halifax studies, and because the levels are similar to the Canadian national average concentration reported by McKeague and Wolynetz (1980), a soil level of 520 µg Mn/g has been selected for cities with no manganese-emitting industries (Montréal and St. John) for the purposes of this assessment. As mentioned above, Forget *et al.* (1994) found no evidence of enhanced total manganese levels in soils exposed to vehicular traffic, a finding they attribute to the negligible amount of soil deposition of manganese compared to the natural manganese content of the soil. It is assumed that the soil manganese level in cities with large manganese-emitting industries (Hamilton and Sault Ste. Marie) is equivalent to 2500 µg Mn/g (Vermette *et al.* 1987).

IV.2.4 Total Manganese Ingestion and Uptake

As explained in section II.1.2, the following assumptions of manganese uptake from the gastrointestinal tract have been made: among adults, manganese uptake from the gastrointestinal tract is 5% and 70% of this is removed through biliary excretion, resulting in an uptake equal to 1.5% of intake; for infants, uptake is equal to intake (100% absorption and 0% removal); and for lack of better data, intermediate absorption of 10% has been assumed for children 7 months-4 years of age, with 70% removal, resulting in uptake equal to 3% of intake.

Estimates of manganese intake from all ingestion sources are presented in Table 11. Values for residents of Hamilton and Sault Ste. Marie are greater than those for residents of St. John and Montréal due to the higher soil manganese levels assumed to occur in towns with industrial sources of manganese. Estimates of total manganese intake range form 0.033 mg/day to 3.73 mg/day depending on age groups and location. For most age groups, manganese from food sources represents the bulk of ingested manganese with the exception of breast-fed infants for whom soil manganese is an important source. This estimate is based on a relatively high assumed of soil intake for children 0-6 months old, which are, to a large extent, immobile.

Estimates of manganese uptake via ingestion are also presented in Table 11. It is evident that manganese uptake is generally less than 4.7 μg/kg bw/day, except among non-breast-fed infants due to high levels of dietary manganese and the assumption of complete uptake from the gastrointestinal tract.

IV.3 Multi-Media Exposure to Manganese

IV.3.1 The General Canadian Population

Total estimated manganese uptake for all age groups and from all media (air, food, drinking water and soil) is presented in Table 12. Total manganese uptake of infants is highly dependent on dietary sources: non breast-fed infants take in much larger amounts of manganese on a body weight basis than do breast-fed infants or any other age group. This is due in part to the complete absorption and inactive biliary excretion assumed for 0-6 month olds.

Fractional uptake of manganese attributable to each media is presented in Table 13. Only breast-fed infants are listed in the table as they have the lowest dietary manganese intake of the four infant diets examined and thus the contribution of air would be maximized. For individuals living in cities with no major manganese-emitting industries, inhalation exposure represents a maximum of 1.1% of daily manganese uptake, and that figure is for the 99th percentile of exposure. Conversely, in Hamilton and Sault Ste. Marie, ambient PM_{10} manganese contributed up to 4% to average manganese exposure, and up to 18% for the 99th percentile of exposure in the population. Thus, in all four cities, for all age groups and for all segments of the population, ambient air does not represent a major source of manganese exposure.

Among breast-fed infants, food and soil are the primary routes of exposure with soil being predominant among the industrial towns. The relatively low contribution from food is associated with the low manganese content of breast-milk, and infants fed formula or "adult" foods would have a substantially higher percentage of intake derived from the diet. The contribution from soil is high for this age category, and is of particular concern in Hamilton and Sault Ste. Marie due to elevated soil levels. It should be noted that the assumed soil consumption rate for infants of 35 mg/day (Health Canada 1994) is high given the relative immobility of this age category. Soil manganese concentrations in St.John and Montréal are based on the natural national average soil concentration (see section IV.2.3) and thus do not reflect manganese that is entirely derived from MMT.

For all other age categories, food represents the principal route of manganese exposure, i.e. 89-96% of average total exposure, and a minimum of 77% for small subsections of the population. Drinking water represents 3-4% of total exposure, which is likely an overestimate due to the documented low levels of manganese in the drinking water of these four cities compared to the assumed value of 100 μg Mn/l (see section IV.2.2). However, this has little effect on the overall assessment of exposure. Soil represents a maximum of only 3% of exposure for individuals over 7 months of age.

Thus, from a multi-media perspective, inhalation exposure represents a very small fraction of total manganese exposure in large Canadian cities with MMT in gasoline and with no major manganese-emitting industries. Similar results were reported by Loranger and Zayed (1994b) for a multi-media exposure assessment of a small number of garage mechanics and blue collar workers in Montréal. In cities with manganese-emitting industries, it is estimated that inhalation exposure may approach 20% of total exposure for small components of the population.

IV.3.2 Populations With High Exposure to Manganese

The above exposure assessment was derived for the general Canadian population, however, it is also of interest to examine individuals or sub-populations with potentially high exposure to manganese. In particular, it is insightful to consider the relative contribution of inhalation to total manganese exposure among "hypothetical" workers exposed to air levels similar to those experienced by the battery-plant workers assessed by Roels *et al.* (1992). These data are presented in Table 14. For each sub-population, the contribution from air, food, drinking water and soil to total manganese exposure are considered.

The inhalation exposures of office workers and taxi drivers are based on 24-hour personal monitoring of the BMRC-defined respirable fraction (see section IV.1.2) by Zayed *et al.* (1994b). Less than 1% of total manganese exposure is derived from air which agrees with estimates for adults in St. John and Montréal provided in Table 12. For the remaining occupational groups, 24-hour exposure has been calculated based on an 8-hour work day and off-work exposure equal to ambient manganese in Montréal, i.e. 0.025 $\mu g/m^3$. The estimate for garage workers overestimates the contribution of air as a source of manganese exposure since as the at-work measure is for manganese in TSP rather than in PM_{10}. In spite of this, it is evident that inhalation exposure represents only 2% of total exposure.

The remaining five categories of workers are based on four categories of at-work manganese exposure experienced by different participants in the Roels *et al.* (1992) study. Specifically, the 92 participants were divided into four quartiles with ascending mean exposures of 101.5 μg Mn/m^3, 196.1 μg Mn/m^3, 216.4 μg Mn/m^3, and 292.3 μg Mn/m^3 (see section V.1 for derivation of these numbers). The average exposure of the whole group was 201.6 μg Mn/m^3. Off-work exposure was assumed to be equal to ambient PM_{10} manganese levels in Montréal and manganese ingestion was set equal to average adult Canadian exposure to manganese through food, water and soil. It is clear that for all four groups of participants, inhalation exposure to manganese represents 86-95% of total manganese exposure (92% for the group as a whole), and thus far outweighs exposure via ingestion in terms of importance. As a group, the battery plant workers are inhaling 12 times more manganese than they are obtaining through dietary sources on a daily basis. This is contrary to what is seen for the general population or for sub-populations exposed to higher than normal levels of vehicular exhaust for whom inhalation exposure is approximately 100 times less than ingestion.

CHAPTER V. ASSESSMENT OF RISK

V.1 Derivation of Reference Values

The initial step in evaluation of the toxicity of environmental contaminants is usually an assessment of their potential for carcinogenicity. In this case, however, the risk assessment has been limited to non-carcinogenic effects, particularly toxic effects on the central nervous system. Results from genotoxicity testing of various manganese salts have been inconclusive; some mutagenicity has been noted in yeasts and certain bacterial strains, and clastogenicity has been noted in several assays (WHO 1981; U.S. EPA 1984; Magos 1991; NTP 1993). Observations over the past century of miners and industrial workers exposed to high levels of manganese-containing dusts in air have not revealed any increased incidence of cancer at levels clearly capable of inducing CNS toxicity. Neurotoxicity is therefore a more appropriate and sensitive endpoint than carcinogenicity.

Of the four epidemiological studies considered in detail, the Roels *et al.* (1992) study was considered to be the most suitable for derivation of an inhalation-specific Tolerable Daily Intake (TDI) since it is the only one of the four in which individual exposures and dose-response information were available. The remaining three studies essentially have only one dose group, however they are useful in providing supporting evidence for the principle study.

All of the available studies have the disadvantage that they are occupational in nature, and are applicable to young (Roels *et al.* 1987a,b, 1992) or middle-aged (Wennberg *et al.* 1992; Mergler *et al.* 1994) white healthy adult males. Their applicability to the general population including women, infants, the elderly, and those made more susceptible by reason of other illnesses, diet, or genetics, can be achieved only by use of uncertainty factors which take these factors into account.

Based on the selected key study (Roels *et al.* 1992) in which increased prevalence of abnormal results for eye-hand co-ordination was observed in workers exposed to manganese (1992), an inhalation-specific Tolerable Daily Intake (TDI) can be calculated, as follows:

Step 1

The No-Observed-Adverse-Effect Level (NOAEL) in this study was **264 $\mu g/m^3$-year** (arithmetic average daily exposure x average no. years exposed for each worker) measured as respirable manganese (approximately PM_{5-7}). This is equivalent to **102 µg/m^3** average exposure per working day (264 µg/m^3-years ÷ 2.6 years), after taking into account that workers in this quartile were exposed for an average of 2.6 years.

Step 2

Inhalation TDI

$$= \frac{102\ \mu g/m^3 \text{ x } 10\ m^3/day \text{ x } 5\ days}{300 \text{ x } 70\ kg \text{ x } 7\ days} = \mathbf{0.035\ \mu g/kg\ bw/day}$$

where:

-10 m^3/day is the quantity of air breathed in an 8-hour work shift, and air breathed during the remainder of the 24 hours is assumed to have negligible manganese concentrations,
-5/7 is an adjustment to account for 5 day exposure per 7 day week.
-70 kg is assumed body weight of the adult males in the critical study
-300 is a composite uncertainty factor:
  x10 for human variability.
  x10 for less than lifetime exposure.
  x$10^{0.5}$ (□3) for other limitations in the database.

Human variability: The principal and supporting studies dealt with young healthy males, the least susceptible group in the population. Infants may be at increased risk because of higher uptake and retention of manganese, and immaturity of the blood-brain barrier; the elderly may be more susceptible to damage to critical areas of the brain (see Section II.5). The average age of workers in the 4 studies was 31.3, 34.3, 43.4 and 46.4 years in the Roels *et al.* (1992), Roels *et al.* (1987), Wennberg *et al.* (1991) and Mergler *et al.* (1994) studies, respectively, and there appeared to be a slight trend to manifestations of toxicity at lower doses as average age in the four studies increased, although interpretation was complicated by differing measures of exposure. In the critical study, the average age of the workers in the fourth, and most affected quartile, was 35.5 years (range 24.6 to 49.6 y), four years older than the overall average age of 31.3 years, but interpretation in this case is complicated by the much higher concomitant exposure levels (292 µg/m^3 average per shift, or three times the level experienced by the first quartile)

Subchronic exposure period: In the Roels *et al.* study (1992), average exposure was only 2.6 years in quartile 1, rising to 8.9 years in the fourth quartile, with the overall average 5.3 years, and duration covaried with extent of exposure by the design of this analysis. Average exposure duration was 7.1 and 16.7 years in the Roels *et al.* (1987) and Wennberg *et al.* (1991,1992) and

Mergler *et al* (1994) studies and there appeared to be a trend towards higher toxicity at a lower dose with increasing duration of exposure, although analysis is complicated by different measurements employed among the studies. (The average duration of exposure in the Wennberg study was 9.9 years but the median was 2.6 years, indicating a strongly skewed distribution with half the workers exposed for a relatively short time). A 10 times uncertainty factor may be too conservative, in view of the lack of direct association between duration of exposure and adverse performance outcomes in the critical study and in the preceding study by the same group (Roels *et al.* 1987a,b; 1992). The U.S. EPA (1994) did not assign an uncertainty factor for duration for this reason.

Limitations in the database: More detailed information is required on the pharmacokinetics of inhaled manganese of the small particle size resulting from automotive combustion, and on toxicokinetics of Mn_30_4 as compared to other valence forms, in particular its disposition in the brain after inhalation exposure. There was some limited evidence that Mn_30_4 is not appreciably more toxic than $MnCl_2$ or $Mn0_2$, but more work is required. The small size of the quartiles in this analysis of the Roels et al. data results in some degree of uncertainty regarding the NOAEL taken from the exposure of the first quartile.

Examination of the individual data supports the hypothesis that a threshold for the appearance of adverse effects is somewhere between 500 and 600 $\mu g/m^3$-year LIRD, or around 150 $\mu g/m^3$ average for an 8-h shift. Grouping of data to give averages always results in loss of precision in the estimation of either LOAELS or NOAELS. This becomes more marked as the groups become large; if the entire cohort is used to give a LOAEL of 793 $\mu g/m^3$, the true LOAEL will be below this value, since it is the average value. The U.S. EPA, in its 1994 assessment for MMT, explored several other options to arrive at an estimation of the equivalent of a NOAEL. The most promising of these was the Benchmark Dose Lower Limit (BMDL) method, in which the lower confidence interval for the dose resulting in a 5 percent increase in responses (considered the background level, or close to this) is calculated; uncertainty factors are then applied as is the case for the NOAEL or LOAEL approach. Using a quantal linear, Weibull restricted or log-logistic model to fit the Roels data, the $BMDL_{0.05}$ values for eye-hand co-ordination were 225, 225 and 173 $\mu g/m^3$-years for the three Roels groupings, and 386, 386, and 324 $\mu g/m^3$-years for the individual data. The value of 264 $\mu g/m^3$-years (□102 $\mu g/m^3$ for an 8-h shift), estimated from the first quartile in this analysis, is in the middle of this range, lending some confidence to these conclusions, despite the small size of the group and the resulting lack of statistical power.

This derived inhalation-specific TDI of **0.035 µg/kg bw/day** is the equivalent of a **tolerable daily uptake** of **0.021 µg/kg bw/day**, assuming a maximum deposition of 60% of fine particulates in the lungs and 100% absorption after deposition (see previous discussion, Section II.1.1).

The 24-hour annual mean air concentration represented by this inhalation TDI is considered to present a negligible risk of adverse neurotoxic effects to all segments of the population, and can be used as a reference point when examining concentrations to which people are exposed. this concentration, C_{air}, is equivalent to the U.S. EPA Reference Concentration (RfC), a better term than the "safe" concentration, since the term "reference" is neutral, and does not imply any absolute safety. (There is no official term in Canada.) The C_{air} is calculated as follows:

$$C_{air} = \frac{0.035\ \mu g/kg\ bw/day \times 70}{23\ m^3/day} = \mathbf{0.11\ \mu g/m^3}$$

where 0.035 µg/kg bw/day is the TDI,
70 kg is the assumed standard adult body weight, and
23 m³/day is the quantity of air breathed daily (Health Canada 1994; ICRP Reference Man, ICRP 1976).

An ambient air value, related to the TDI, can also be directly calculated from the NOAEL of 264 µg/m³-year measured as respirable manganese (approximately PM_{5-7}). This is equivalent to 102 µg/m³ average current daily exposure, after taking into account that workers in this quartile were exposed for an average of 2.6 years. Further adjustment of this NOAEL to a continuous exposure (24-hour, 7 days per week) gives a value of **32 µg/m³**:

$$102\ \mu g/m^3 \times 10/23\ m^3/day \times 5/7\ days = 31.7\ \mu g/m^3/day.$$

Workers are assumed to breathe 10 m³ of air during a work shift (ICRP 1976).

The air concentration that would be expected to be protective with respect to the induction of human health effects would therefore be:

$$C_{air} = \frac{32\ \mu g/m^3}{300} = \mathbf{0.11\ \mu g/m^3} \text{ for respirable manganese } (PM_{5-7})$$

where 300 is the selected uncertainty factor for the reasons given above. The PM_{5-7} refers to a manganese particle size intermediate between the fine particulate matter ($PM_{2.5}$) and PM_{10} currently measured in ambient sampling programs in Canada.

The air concentration thus derived is remarkably similar to a number of derivations by the U.S. EPA using the Benchmark Dose (Lower Limit) approach ($BMDL_{10}$ or $BMDL_5$ for 10 or 5 percent response) with various models to estimate and fit curves. Other techniques such as Bayesian analysis with both continuous and dichotomous data, and "No statistical significance of trend" or Nostasot approach also yielded estimates in the range 0.09 to 0.2 $\mu g/m^3$, which was quoted by EPA (U.S. EPA 1994) as the best estimate range for a new Reference Concentration for respirable manganese (given in that document as PM_5).

V.2 Risk to Canadians

Ambient levels of respirable manganese

For cities without large manganese emitting industries, ambient levels of respirable manganese are associated with the size of Canadian urban centres, with the larger cites (eg. Montréal, Toronto and Vancouver) having the highest annual means (0.020-0.025 $\mu g\ Mn/m^3$). Based on 1992 data, the mean annual PM_{10} manganese concentrations in all major urban centres without manganese emitting industries are less than 25% of the reference level (C_{air}) of 0.11 $\mu g\ Mn/m^3$. Contrary to this, annual arithmetic mean levels of PM_{10} manganese in areas adjacent to industrial centres in Hamilton and Sault Ste. Marie are at or above C_{air}.

Canadian Personal Exposure Studies

Several studies of personal inhalation exposure to manganese (either in TSP or respirable particulates) have been carried out in Canadian cities, the results of which are provided in Fig. 12. Although these studies were not designed to be statistically representative of a specific population, the findings show consistently that personal inhalation exposures to manganese are less than 30% of C_{air} (0.11 $\mu g/m^3$) for either respirable or total suspended particulates, and including estimates for sub-populations likely to be exposed (eg. taxi drivers). The only exception is for garage mechanics whose 24-hour personal exposure is estimated to be 0.085 (TSP), i.e. 77% of C_{air}: as discussed in section IV.1.2, this includes exposure under inadequate ventilation conditions: under ventilated conditions, 24-hour exposure of garage mechanics is 0.054 $\mu g/m^3$, i.e. half of C_{air}). The personal exposure monitoring data from the PTEAM study indicate that the residents of Riverside, California, are, as an average, currently exposed to 40% of C_{air}, while the 95th (0.10 $\mu g/m^3$) and 99th (0.21 $\mu g/m^3$) percentiles of the population approach and exceed the C_{air}, respectively (note that this is based on the current situation in which the use of MMT in unleaded fuel is not allowed). These data suggest that manganese exposure, possibly as it relates to particle size, sources or human activity are substantially different in Riverside, California than in the Canadian cities studied to data.

Estimates of Canadian exposure to PM_{10} manganese based on ambient monitoring data

Four urban areas were targeted for this exposure assessment: St.John (a small city with moderate traffic levels and no manganese-emitting industry); Montréal (a large city with high traffic levels and no manganese-emitting industries); and Hamilton and Sault Ste. Marie (both with major manganese-emitting industries and very high ambient levels of respirable manganese). The ambient monitor recording the highest level of PM_{10} manganese were selected for each city. Five age categories (0-6 months; 7 months-4 years; 5-11 years; 12-19 years; 20 years and over) were considered, and the arithmetic mean, 90th percentile and 99th percentile were examined in each case.

The mean, 90th percentile and 99th percentile of ambient manganese exposure in St. John and Montréal are well below the reference level of 0.11 $\mu g/m^3$: even the 99th percentile in Montréal is less than half of this level at 0.041 $\mu g/m^3$ (Table 4). However, the mean concentrations near the industrial centres of Hamilton and Sault Ste. Marie are at or exceed C_{air}, the 90th percentiles are 2-4 times greater than C_{air}, and the 99th percentiles are 3.5-8 times greater than C_{air}.

An inhalation tolerable daily uptake (*tdu*) of 0.021 µg Mn/kg bw/day was derived in section V.1, assuming 60% deposition of inhaled particulates. Mean inhalation uptake of manganese in St. John and Montréal ranges from 10-33% of the inhalation *tdu*, while the 99th percentile of exposure in those cities represents an uptake of 20-50% of the *tdu* (Table 5). Mean uptake of manganese in Sault Ste. Marie and Hamilton is equivalent to or exceeds the *tdu*: the 99th percentile of exposure is equivalent to 3-10 times the *tdu*.

Estimates of Canadian inhalation exposure to PM10 manganese based on extrapolation from the PTEAM study

The population distribution of personal exposure to PM10 manganese reported in the PTEAM study conducted in Riverside, California, was applied to ambient mean concentrations of manganese in the four Canadian target cities. As discussed in section IV.1.2, inspite of the uncertainty in this extrapolation, it provides an indication of personal exposure among the upper percentiles of the population. Mean population exposures will be identical to those based on the ambient means. Considering St. John and Montréal, only 1% of the population living near the Montréal monitor at the Décarie Expressway are estimated to experience levels comparable to C_{air};

in fact, exposures of the 90th percentiles and the 99th percentile in St. John do not exceed C_{air} (Table 6). Thus, one can conclude that in large cities with MMT in use as a gasoline additive but with no large manganese-emitting industries, exposure of the entire population is estimated to be below the reference level (C_{air}), and for 90% of the population below half of the reference level. The 90th and 99th percentiles of personal exposure in Hamilton and Sault Ste. Marie are generally less than those estimated using the ambient monitoring data, with the exception of the 99th percentile in Hamilton. Mean exposure is at or exceeds C_{air}, and the upper percentiles are 1.7-6.8 times C_{air}.

Compared to the inhalation *tdu* of 0.021 µg/kg bw/day, mean inhalation uptake in St. John and Montréal are estimated to be 10-30% of this value, similar to the results from the ambient monitoring data (Table 7). The 90th percentile of exposure in those two cities ranges from 15-50% of the *tdu*, and the 99th percentile of exposure from 40-150% of the *tdu*. For Hamilton and Sault Ste. Marie, mean inhalation uptake is at or above the *tdu*, the 90th percentiles are 1.5-4 times the *tdu*, and the 99th percentile is 4-10 times the *tdu*.

Multi-media exposure to manganese

As a final analysis, inhalation uptake of PM_{10} manganese has been considered from a multi-media perspective. Fractional uptake of manganese from air, food, water and soil are presented in Table 13, for each of five age groups in the four target cities, for which inhalation exposure is based on ambient air monitoring data. In cities with no industrial sources of manganese, mean inhalation uptake for all age groups is less than 1%: this includes exposure of individuals living in a highly trafficked location in Montréal (the Décarie Expressway at the Métropolitain). Although not presented in this table, even the 99th percentile of inhalation exposure based on the estimates of personal inhalation exposure represents a maximum of 2% of total manganese uptake in St. John and Montréal. In cities with large manganese-emitting industries, inhalation represents up to 4% of average manganese exposure, and up to 18% for the upper percentile of the population. It should be noted that this percentile represents the top 1% of exposure among the population living in the area immediately adjacent to the industries. Among occupational groups that might be especially exposed to vehicular derived manganese, a maximum of 2% of total dose (for garage mechanics) is derived from inhalation (Table 14). This suggests that the garage workers are typical of the upper percentile of population exposure in large Canadian cities with no manganese-emitting industries. Conversely, for battery plant workers similar to those studied by Roels *et al.* (1992), inhalation uptake represents over 90% of total manganese uptake. Considering all the job categories in Table 14, only the battery plant workers experience inhalation exposure to manganese above (230-650 fold) the inhalation tolerable daily uptake of 0.021 µg Mn/kg bw/day.

V.3 Conclusions

Based on ambient monitoring data, the inhalation intake of all components of the population in Canadian urban centres where there are ***no major manganese-emitting industries*** is less than 50% of the Tolerable Daily Intake. Based on estimates of personal exposure, the 90th percentile of exposure for all age groups is less than 50% of the Tolerable Daily Intake. This TDI is considered to be a conservative estimate.

Current levels of airborne respirable manganese to which the population in large Canadian urban centres are exposed, are **below** the benchmark air level at which no adverse health risks are expected. This assessment includes infants, the elderly and those more heavily exposed than average because of their occupation or their proximity to roads.

No correlation was evident between levels of ambient respirable (PM_{10} or $PM_{2.5}$) manganese and MMT sales or use in unleaded gasoline, whether examined by geographical area or by season, in spite of the substantial changes in MMT use that have occurred. City size, traffic density and vehicle-related activities are consistently associated with elevated ambient levels of respirable manganese, suggesting that some vehicle-related factors are contributing to manganese exposure, possibly unrelated to direct vehicular emissions.

It has therefore been concluded that airborne manganese resulting from the combustion of methylcyclopentadienyl manganese tricarbonyl (MMT) in gasoline powered vehicles is not entering the Canadian environment in quantities or under conditions that may constitute a health risk.

For cities in which there are ***major manganese-emitting industries*** (for example steel mills), average respirable manganese exposure of the population is **at or above** the tolerable level at which it has been calculated that the risk of adverse health effects may begin to increase. This was deemed to be unrelated to the combustion of MMT in gasoline.

While the focus of this report was on airborne combustion products of MMT, it was concluded that MMT itself is not found in sufficient quantity or for a sufficient length of time in the atmosphere to be considered a threat to human health. Other routes of exposure, in particular the dermal route for occupational or solvent exposure, were beyond the scope of this assessment.

V.4 Recommendations

Given that respirable manganese exposure of 10% of the population in high traffic areas may be greater than 50% of the Tolerable Daily Intake, it is recommended that exposure of the population of Canada to airborne respirable manganese be closely monitored, with emphasis on personal monitoring of susceptible populations and high-exposure groups, and on ambient monitoring of microhabitats such as parking garages with potentially high levels of manganese.

Because it is not known at this time what the sources of this manganese are, more work is required to identify the sources of manganese, by means of more precise and current emissions inventory data along with source apportionment studies.

Additional ambient air monitoring is required in cities where major manganese-emitting industries are located. Data are required on the chemical speciation, particle size distribution of respirable manganese, and on the population distribution of personal exposure.

It is recommended that additional ambient air monitoring for MMT itself be conducted, due to the substantial increase in MMT use since previous sampling (1979). Specifically, the levels of MMT at gasoline retail outlets and at street level in urban centres are required.

Based on information found for this report on exposure of mechanics in service garages, it is recommended that employees of vehicle service garages be advised to reduce exposure to vehicular exhaust where possible, as well as dermal exposure to unburned MMT through solvent use of gasoline.

Based on new information on the genotoxicity of MMT itself, an assessment of its dermal toxicity and potential risk to health from this route of exposure should be carried out.

CHAPTER VI. SUMMARY

MMT, or methylcyclopentadienyl manganese tricarbonyl has been used in Canada since 1976 to raise the octane rating of gasoline. The phase-down and phase-out of alkyl lead additives completed by December 1990, has resulted in greatly increased use of MMT in the last decade.

The major health concern arises, not with MMT itself (which was not specifically addressed in this review), but with the airborne manganese oxides produced upon combustion of the additive. Manganese, although considered an essential element in small amounts, is neurotoxic at higher doses, particularly when inhaled, since self-limiting homeostatic mechanisms are most effective for manganese derived from gastrointestinal uptake.

Manganese is a ubiquitous element both in the environment (soil, water, food, and air) and in biological systems, where it is normally present in all tissues in varying concentrations. Manganese is an essential element required for the function of a number of enzymes, although it appears that the requirements for humans are lower than those for several other mammalian species. This essentiality means that small doses are not toxic and are well handled by the body.

Metabolic data indicate that exposure and uptake via inhalation are also to a certain extent controlled by the liver, with a partial "first pass" effect. However, the degree of uptake via this route is greater by at least an order of magnitude than uptake via the gastrointestinal tract, which averages around 3 to 5 percent of an administered dose. Clearance from the lungs, brain and other areas of the body may be much slower after inhalation exposure than after oral exposure, thus allowing some accumulation to take place during chronic inhalation exposure, which could provide a reservoir of manganese ions. Brain manganese levels are therefore more influenced by excessive inhalation intake than by high intake through the gastrointestinal tract.

Infants have been targeted as a particularly high risk group, since their metabolic mechanisms for maintaining manganese homeostasis are undeveloped at birth, thus allowing for greater uptake and retention from all routes of exposure. Their blood-brain barrier is also poorly developed, thus allowing ingress to manganese ions to their CNS, which is still undergoing development, thus presenting a vulnerable target for metal toxicity. Evidence from animal studies supports the hypothesis that excessive doses of manganese from whatever source can lead to an overload and deposition of manganese in the brains of infants and the appearance of subclinical signs of CNS dysfunction.

The elderly may be at increased risk from excessive exposure to manganese, due to increased susceptibility of aging brain cells to injury, added to the "normal" slow loss of neurons as neuron age increases. The dopamine pathways in the basal ganglia are thought to be highly susceptible to age-related neuronal attrition, thus overcoming the considerable functional reserve capacity and leading to long delayed effects, as well as to insult from xenobiotics. In one of the few recorded human cases of manganese intoxication via drinking water, the severity of the symptoms increased with increasing age, while children were unaffected.

The importance of chemical speciation of the manganese ion at intake is unclear. Mn_3O_4 is composed of one divalent (Mn^{2+}) and two trivalent ions (Mn^{3+}). The latter is in a more oxidized form, is very reactive, and is believed to be responsible for much of the toxic action on the dopamine system in the brain. Delivery of manganese to various tissues and cells is at least partially dependent on its ionization state. Some Mn^{2+} appears to be converted to Mn^{3+} and carried across cell membranes via transferrin, in the same way as oxidized iron, Fe^{3+}. However, Mn^{3+} from inhalation intake would be readily available to the circulatory system without any need for conversion. Studies in animals, in which several different valence forms of manganese were administered via several routes, suggest that manganese chloride and other soluble species are initially more toxic than the oxides, although some differences were noted in clearance times from various tissues, and final equilibrium concentrations after uptake of Mn^{3+} could be as high as or higher than those after uptake of Mn^{2+} ions.

Chronic inhalation exposure in occupationally exposed workers in mining and processing of manganese ores to high concentrations of airborne manganese dust has been known for at least a century to result in a condition known as manganism, with many neurological symptoms similar to those seen in Parkinson's Disease. Lesions of the central nervous system occur in the striatum and the globus pallidum, with some damage often seen also in the substantia nigra. Manganese is believed to exert its effects through the dopaminergic pathway, by lowering tissue concentrations of the neurotransmitter dopamine, resulting in the eventual death of brain cells.

Several newer epidemiological studies on workers occupationally exposed to relatively low levels of manganese dust were examined, in order to derive a Tolerable Daily Intake and an associated 24-hour air concentration to which all segment of the population could be exposed without appreciable risk of adverse neurotoxic effects.

These studies suggested that cumulative exposure to respirable manganese dust (measured as various particle sizes from less than 2.5 to 10μm) at levels in the range 550 to 800 $\mu g/m^3$-year, equivalent to 35 to 200 $\mu g/m^3$ current time weighted average exposure for 8-hour shifts, resulted in the first subtle signs of impairment of motor function, reaction time, speed and co-ordination.

The cross-sectional study by Roels *et al.* (1992) is the only one of the four studies that was considered to be suitable for the derivation of an inhalation-specific Tolerable Daily Intake (TDI), since individual exposures to respirable manganese and dose-response information was available. However it shares the disadvantage of the remaining studies in that they are occupational in nature and are applicable to young or middle-aged white healthy males. Uncertainty factors are required to account for susceptibility of several subpopulations, notably infants and the elderly.

A No-Observed-Adverse-Effect Level (NOAEL) of 264 μg/m^3-year, converted to an annual 8-h average of 102 μg/m^3, was used to derive an inhalation-specific **Tolerable Daily Intake of 0.035 mg/kg body weight/day.** A Tolerable Daily **Uptake of 0.021 mg/kg b.w./day** is calculated to be equivalent to the TDI of 0.035 mg/kg b.w./day. The **24-hour annual mean air concentration** represented by this inhalation TDI **is 0.11 μg/m^3 (C_{air})** for respirable manganese (PM_{5-7}).

These three values were then used to compare to Canadian exposure to and uptake of respirable manganese. Exposure of Canadians to ambient manganese was assessed, and the following conclusions can be drawn for Canadian cities with no major manganese producing industries.

Levels of respirable manganese in major Canadian urban centres have remained constant or decreased from 1986 to 1992, and do not reflect major changes in MMT use during that time, suggesting that MMT does not contribute substantially to ambient urban PM_{10} or $PM_{2.5}$ manganese concentrations. It is impossible to ascertain the influence of MMT on ambient manganese levels in the submicron fraction at this time. Similarly, significantly higher concentrations of respirable ambient manganese in winter than in summer are unrelated to MMT use which is higher in the summer. However, large city size, high traffic density and vehicle-related activities are associated with higher levels of respirable manganese, possibly unrelated to vehicular emissions.

Concentrations of ambient manganese in Canadian cities are at most 25% of the C_{air} reference level. Studies of personal exposure to manganese in Canadian cities indicate that for the groups studied, outdoor stationary ambient monitors overestimate personal exposure, possibly due to the lower manganese levels indoors and the disproportionate amount of time spent indoors by people. The only exception to this is garage mechanics. Personal exposures of all groups studied are less than 50% of the C_{air} reference value of 0.11 μg/m^3.

The mean, 90th percentile and 99th percentile of ambient PM_{10} manganese in high traffic areas are substantially below C_{air}, and based on these levels inhalation exposure to manganese is less than half the Tolerable Daily Intake for all age groups in the Canadian population. Estimates of personal exposure to manganese in Canadian cities (based on extrapolation from the PTEAM study) indicate that up to the 90th percentile of the population are exposed to less than half of C_{air}, and an inhalation manganese intake less than half of the Tolerable Daily Intake.

From a multi-media exposure perspective, inhalation represents less than 2% of total daily uptake of manganese for all age groups and all percentiles of the population, as well as occupational groups such as taxi drivers and service garage mechanics. The remainder is derived primarily from natural levels of manganese in dietary sources. For individuals exposed to very high levels of manganese in an occupational setting (eg. battery plant workers), air represents more than 90% of total manganese exposure.

Thus, all analyses indicate that the combustion products of MMT in gasoline do not represent an added health risk to the Canadian population.

In addition, inhalation exposure to manganese has been assessed for residents of cities with large manganese-emitting industries such as steel mills. Current mean ambient air manganese levels are at or substantially above 0.11 $\mu g/m^3$ (C_{air}), and the 90th and 99th percentiles of exposure can be much higher (up to 0.23-0.83 $\mu g/m^3$). Similarly, inhalation uptake for all age groups approaches or exceeds the *tdu*. This raises concern regarding chronic exposure to manganese for residents in these cities, and recommendations are made regarding this issue.

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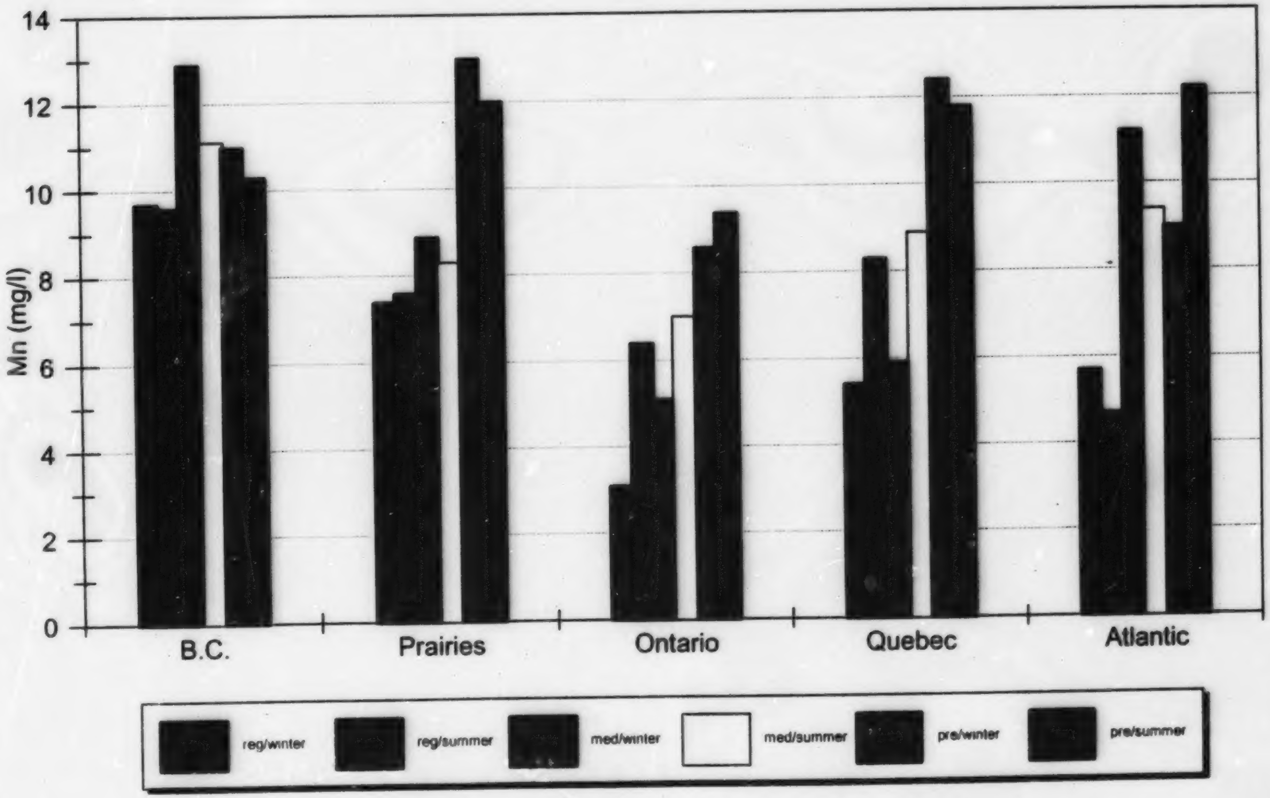
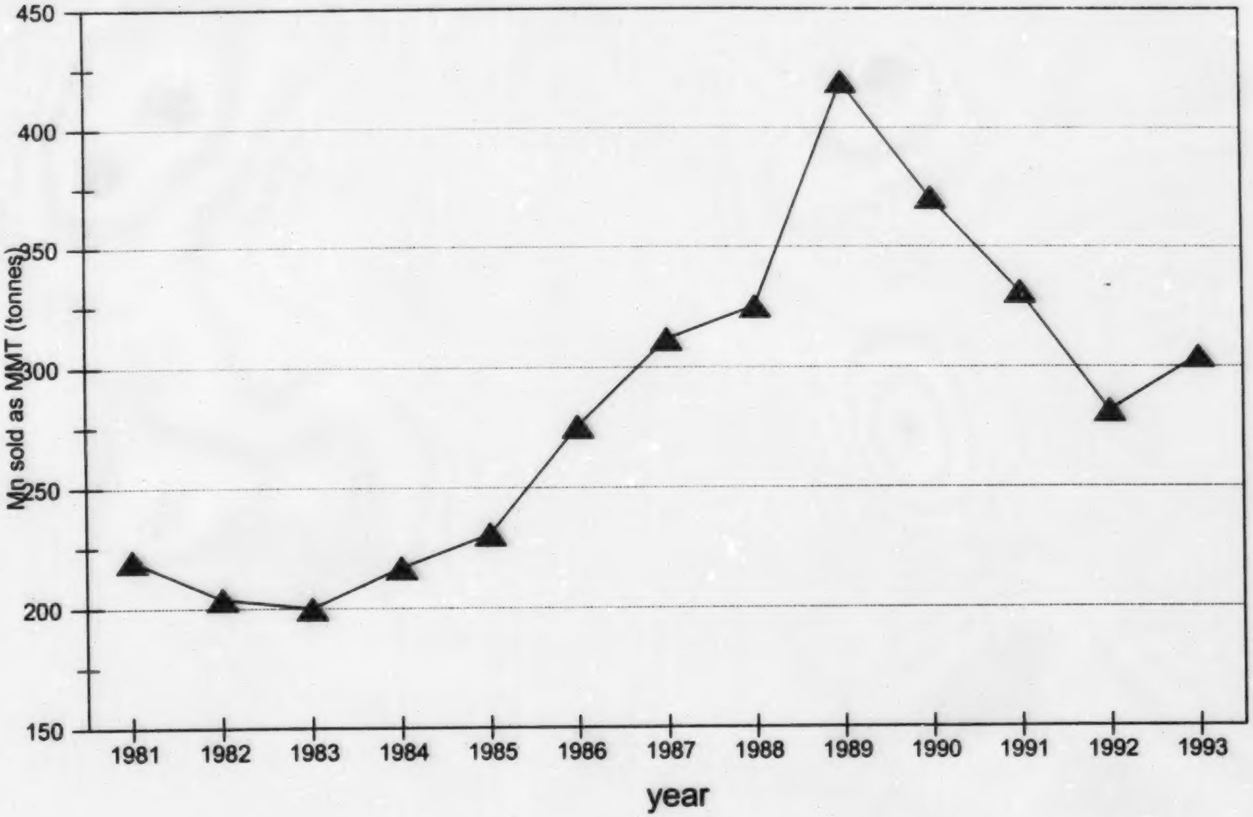
Fig.1. Mn in Canadian gasoline in 1993

(regular, medium and premium blends)



Based on data in CPPI (1994)

Fig.2. Manganese sold as MMT in Canada



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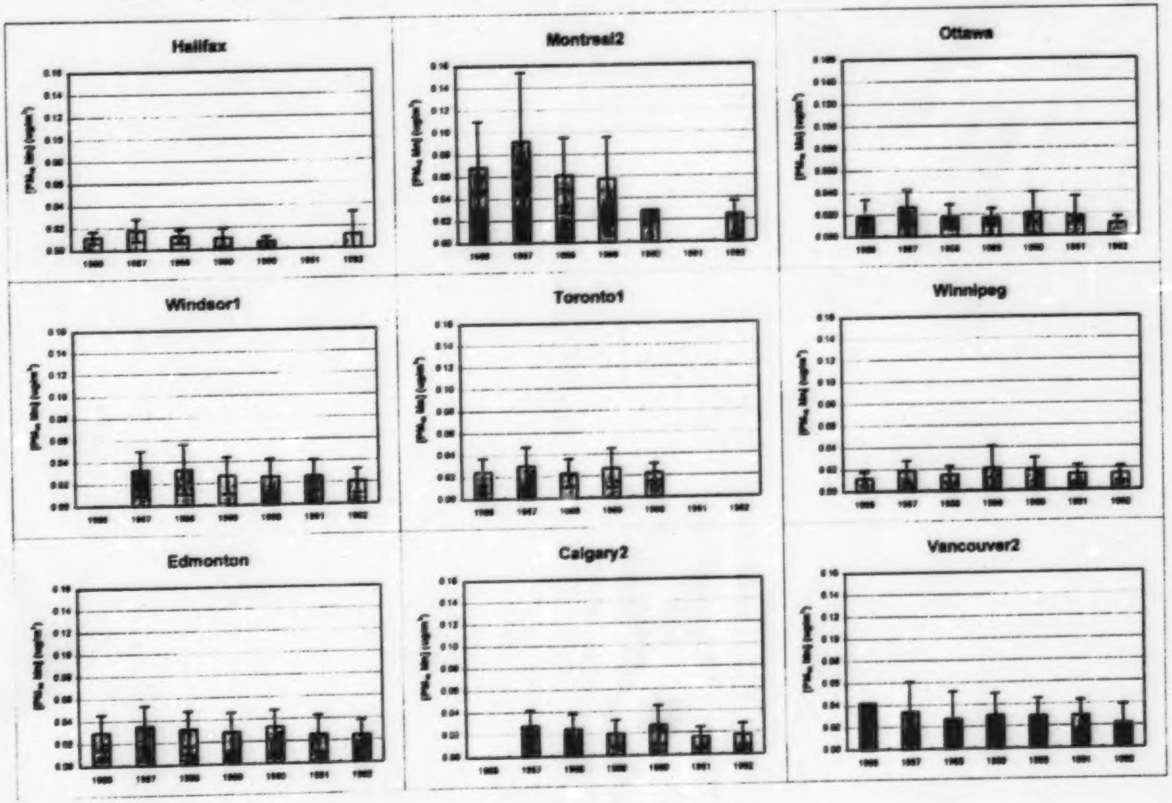
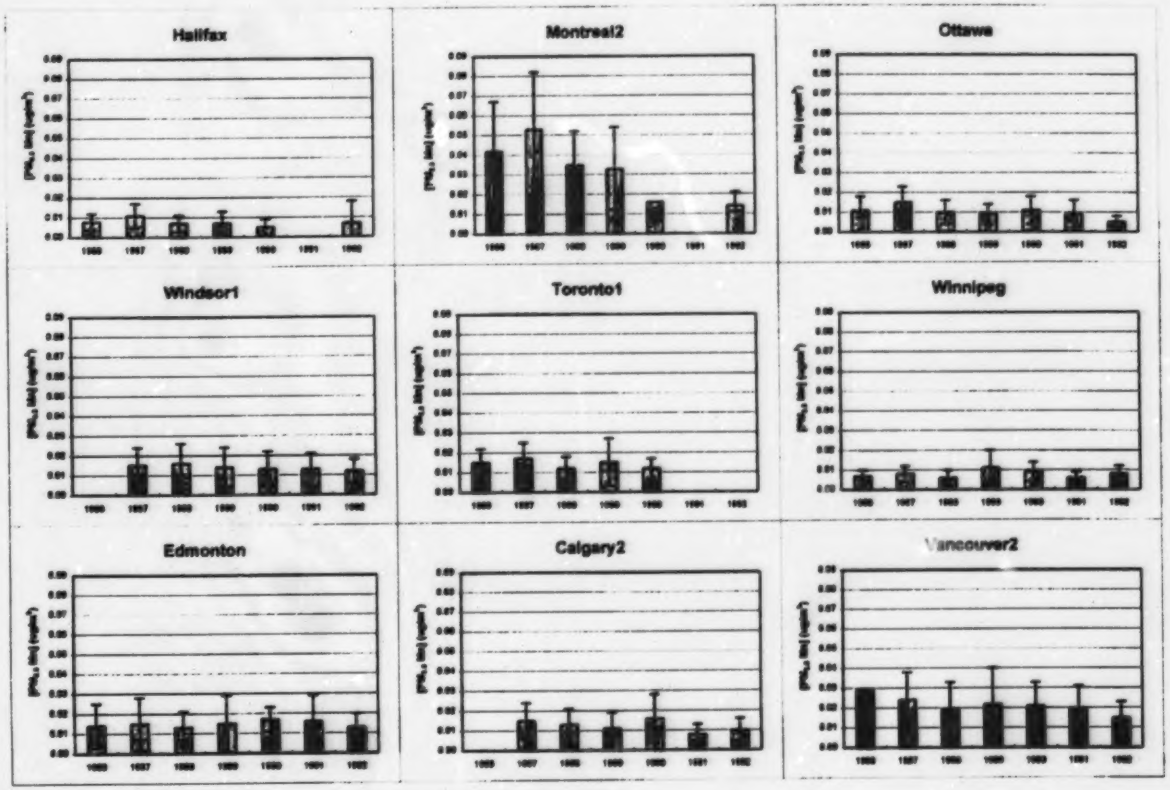
[2] Data represent Ethyl Corp. sales only (provided by Wilson 1994)

Fig. 3. Trends in ambient PM_{10} manganese levels in Canadian cities (1986-1992)



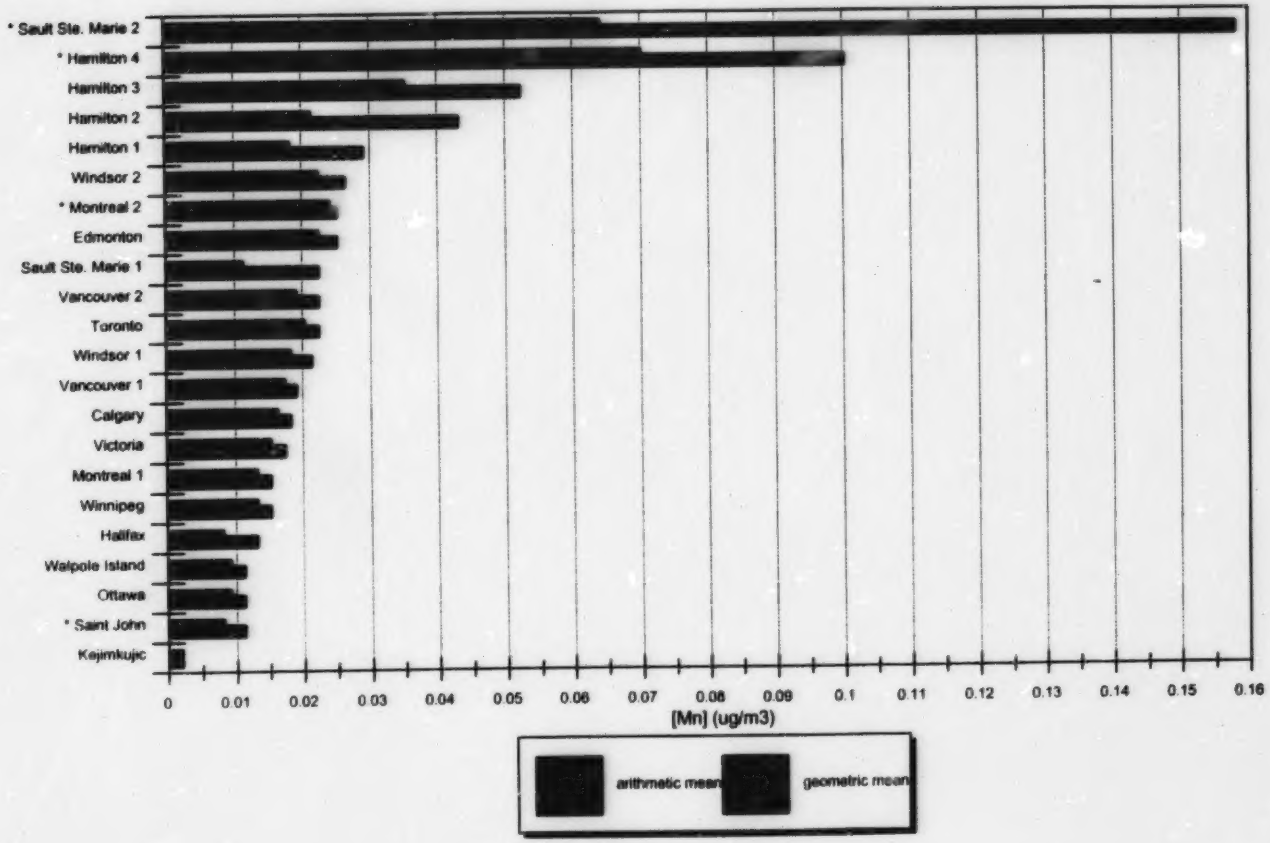
arithmetic mean +/- s.d.: based on original data provided by T. Dann (1994b)

Fig. 4. Trends in ambient $PM_{2.5}$ manganese levels in Canadian cities (1986-1992)



arithmetic mean +/- s.d.: based on original data provided by T. Dann (1994b)

Fig.5. Annual mean PM10 manganese in ambient air (1992)[3]



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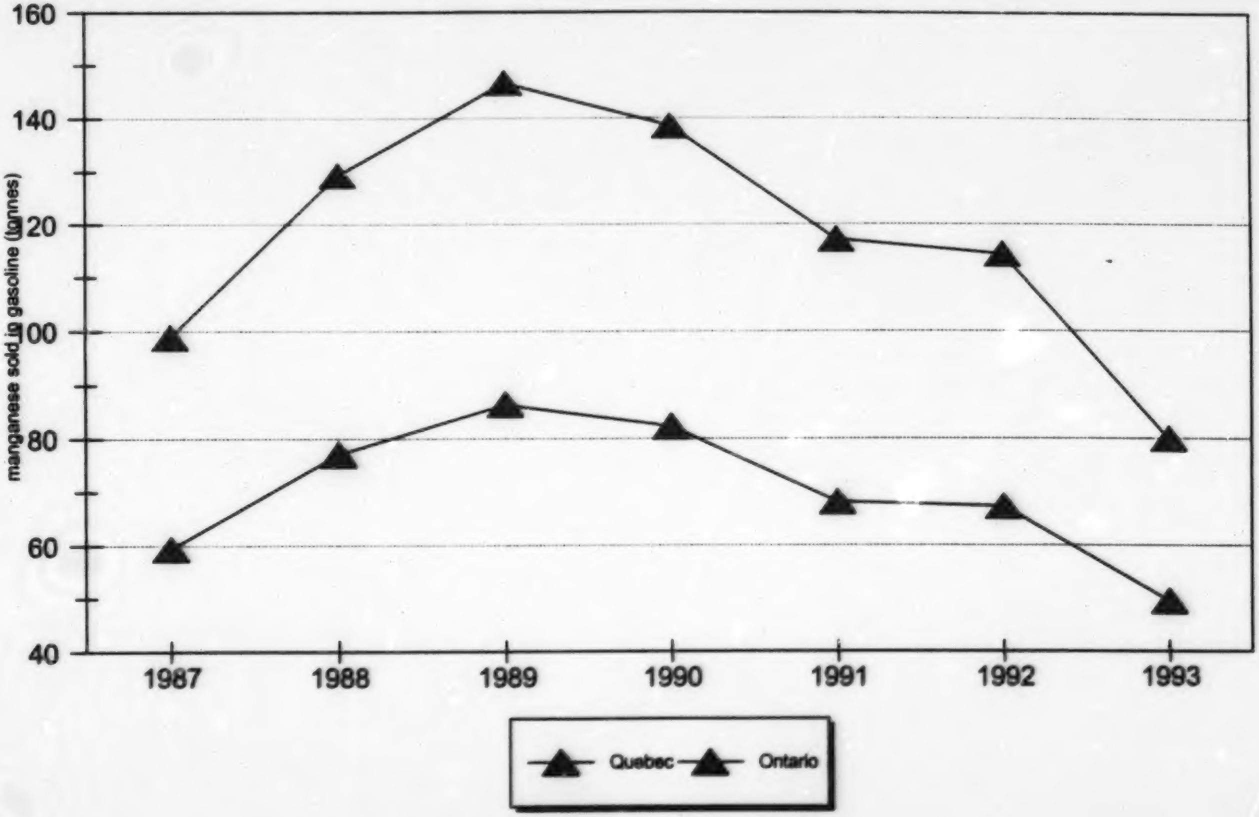
[3] *=sites used in exposure assessment. Data from OMOEE (1993) and from original data provided by Dann (1994b).

Fig. 6. Manganese sold as MMT in
unleaded gasoline in Quebec & Ontario



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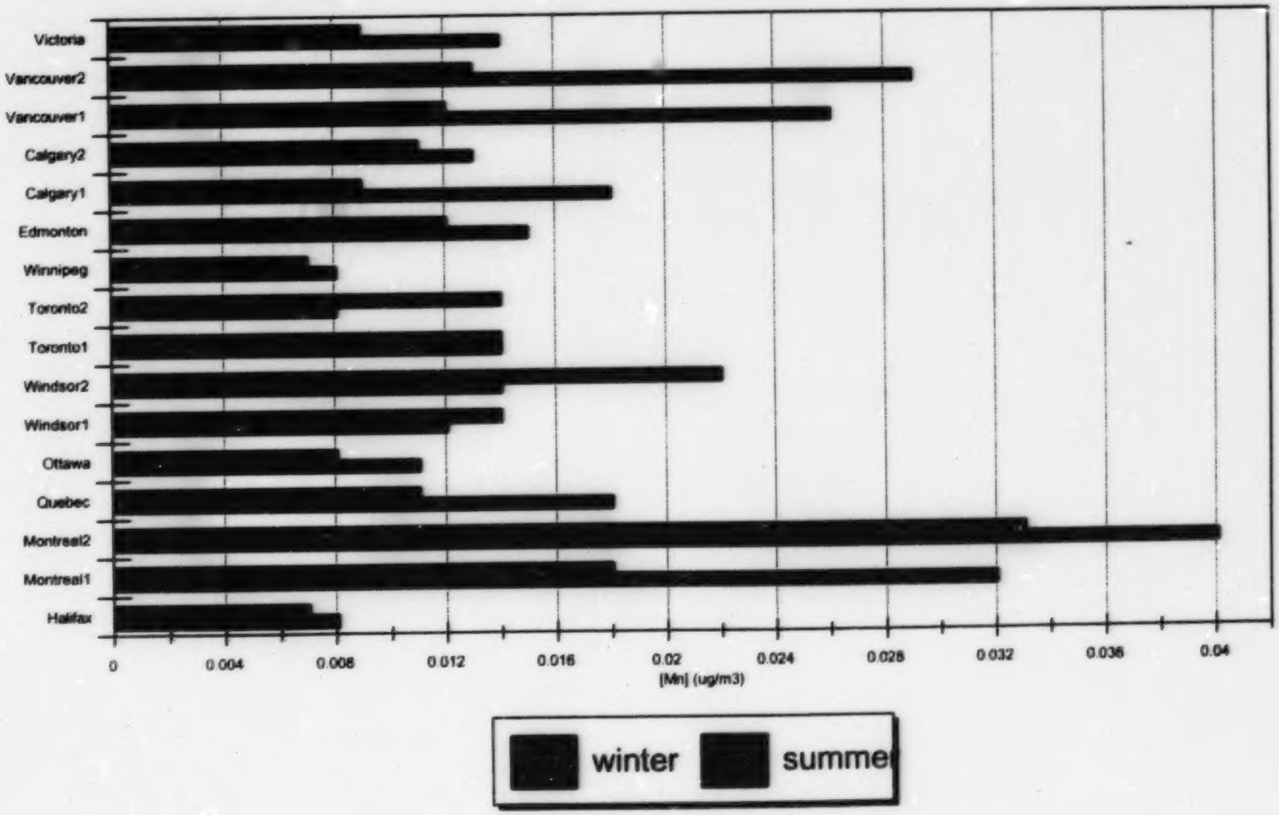
[4] Based on fuel sales including leaded premium fuel

Fig.7. Annual mean PM2.5 manganese (1986-1993) in winter and summer[5]



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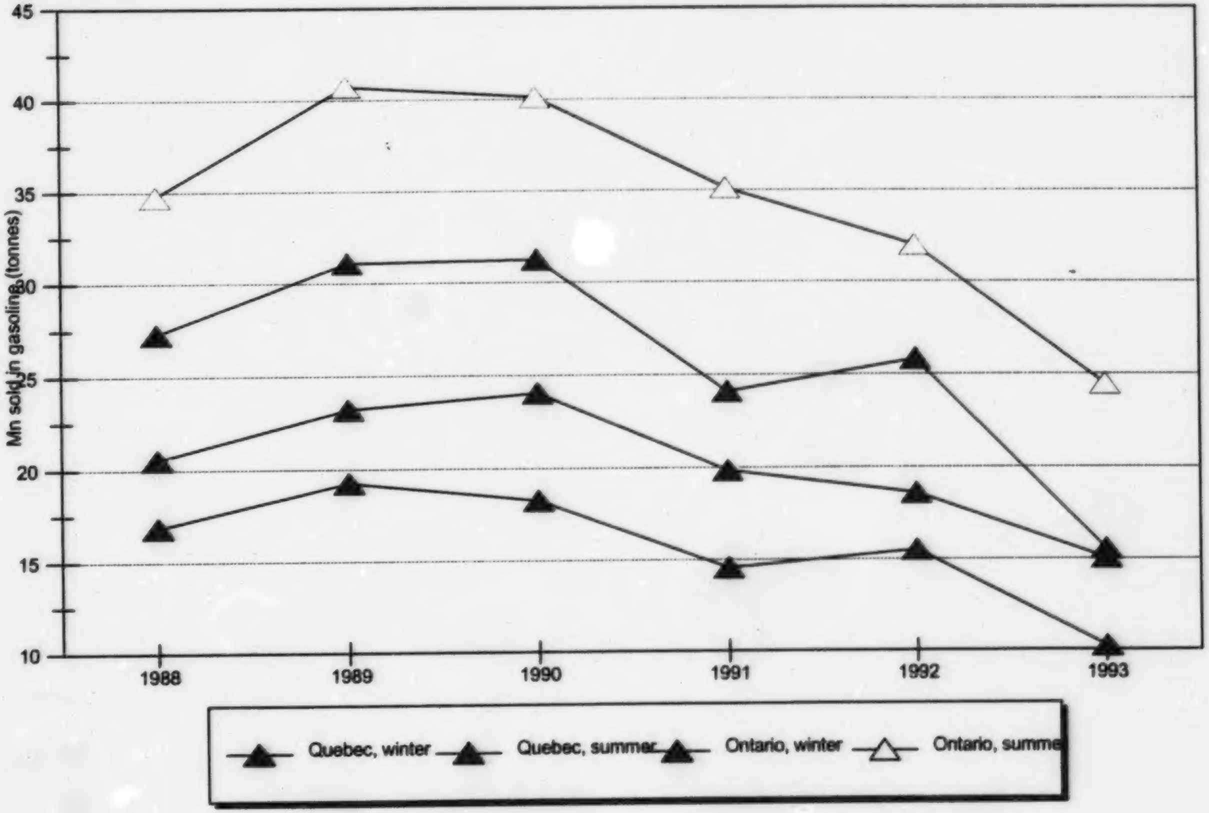
[5] Winter=December, January, February; summer=June, July, August; means are annual arithmetic means

Fig.8. Seasonal patterns of MMT use in[6]

Quebec and Ontario



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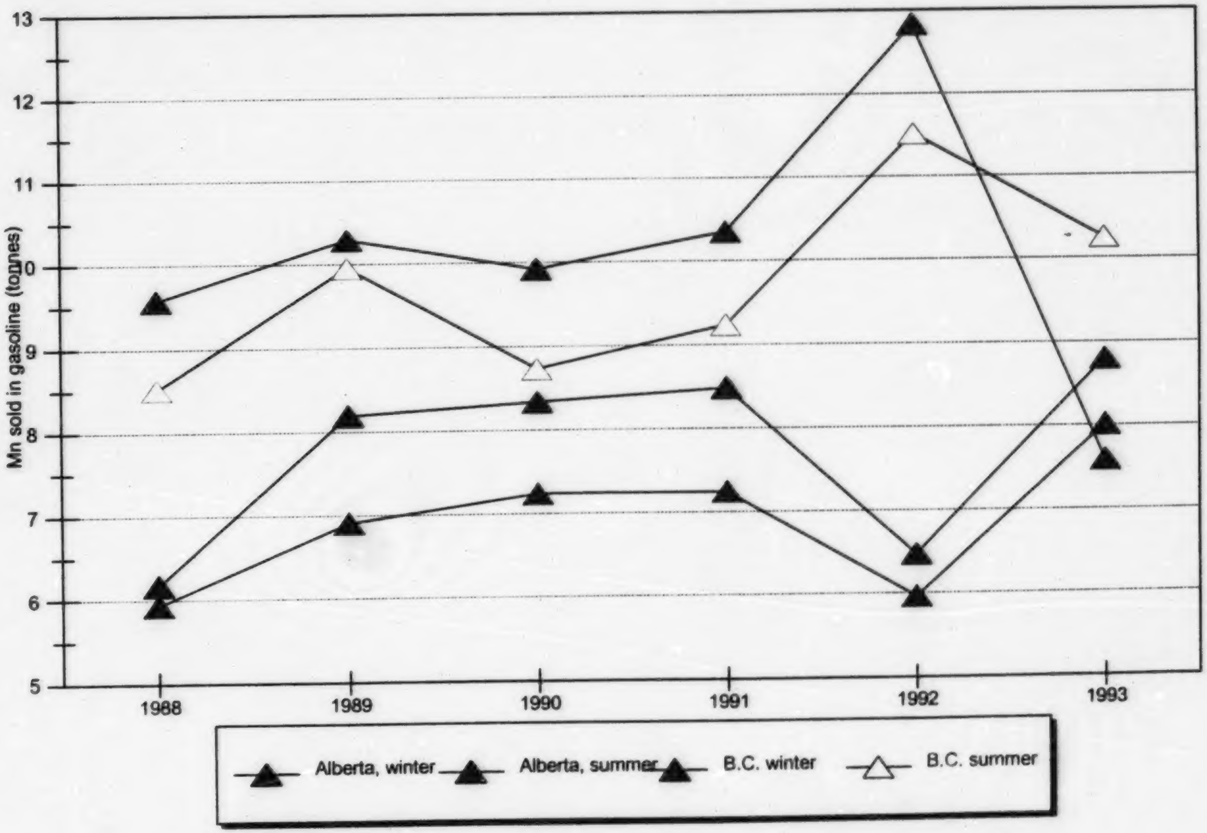
[6] Winter=December, January, February; summer=June, July, August

Fig.9. Seasonal patterns of MMT use in[7]

Alberta and British Columbia



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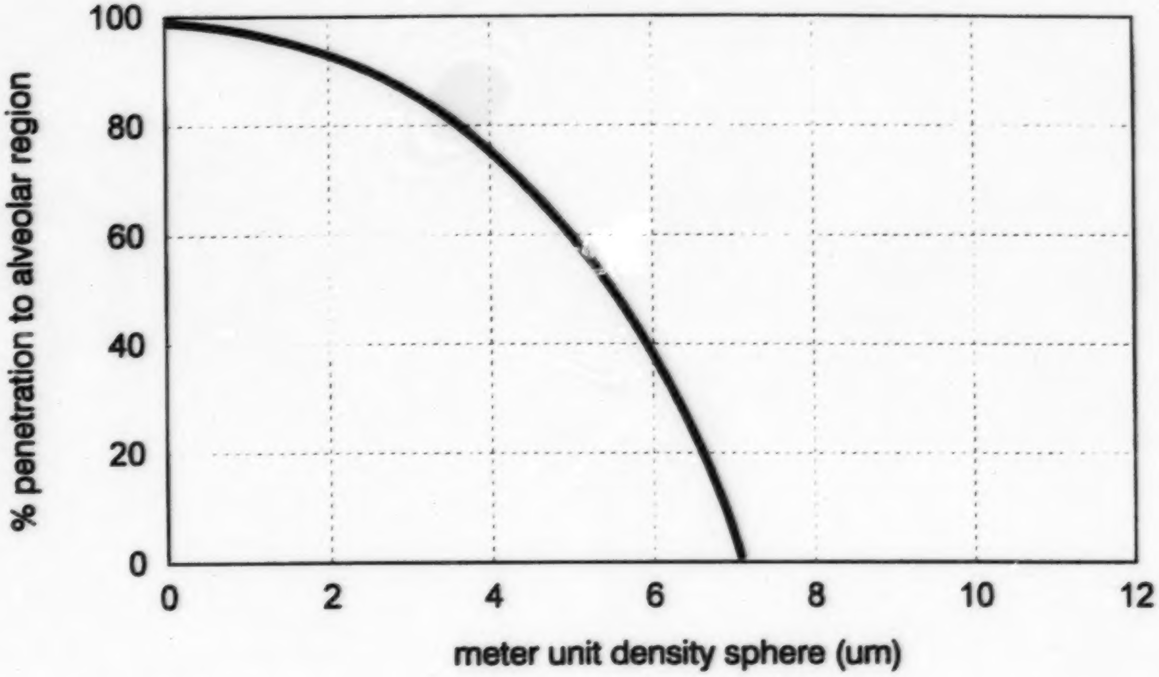
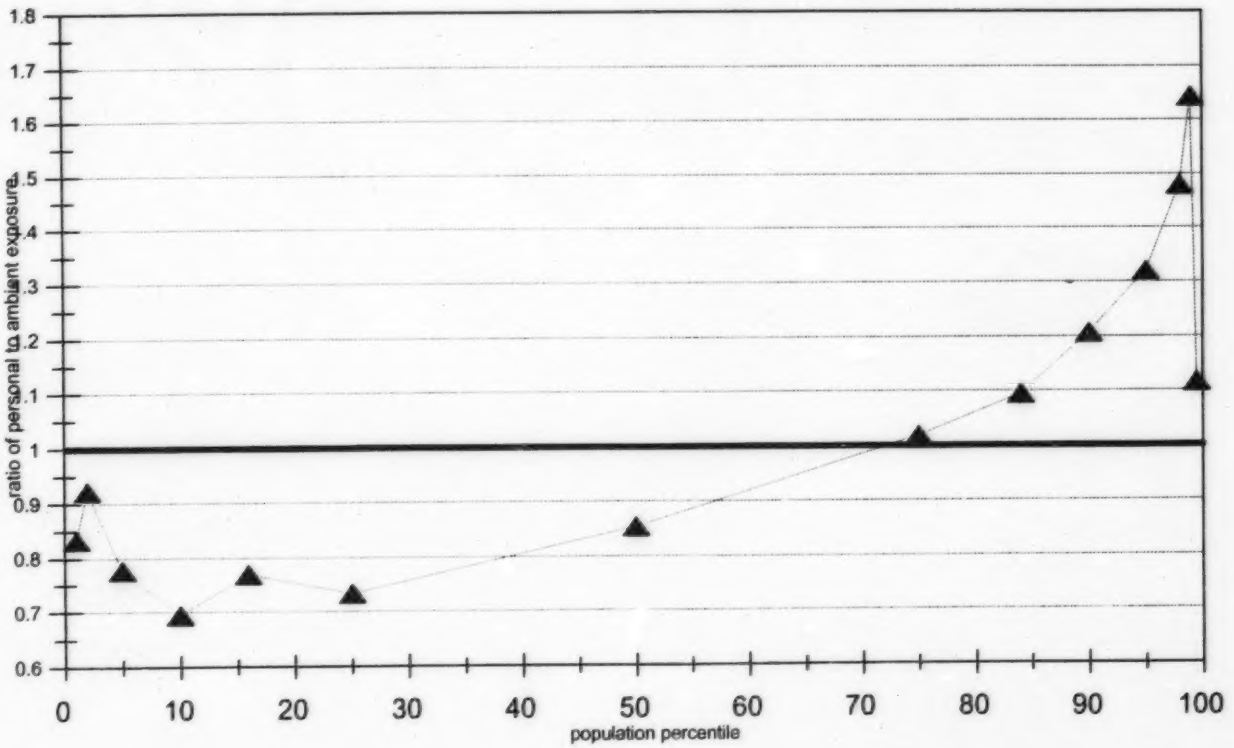
[7] winter=December, January, February; summer=June, July, August

Figure 10. BMRC defining curve for respirable particulates



Adapted from ACGIH (1971)

Fig.11. Ratio of personal to ambient PM10 Mn exposure in Riverside, CA[8]



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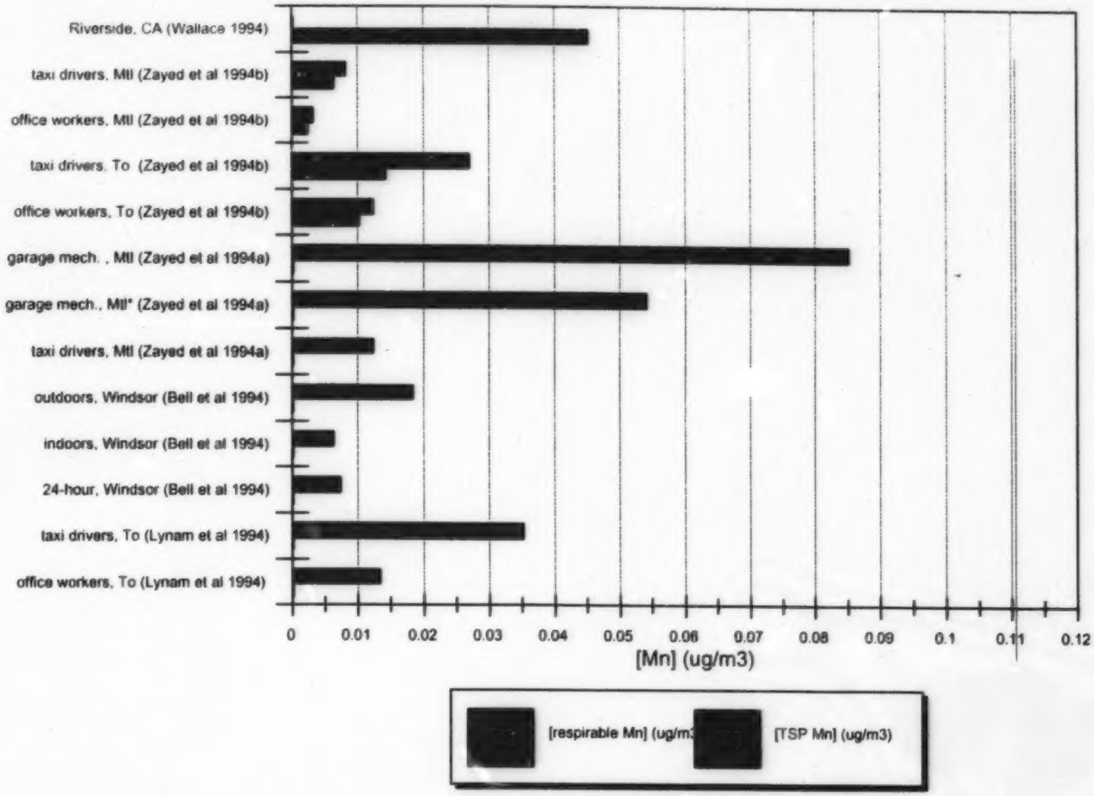
[8] Based on 24-hour monitoring data of PTEAM study

Fig.12. Estimates of 24-hour personal exposure to manganese



[9] *Under ventilated conditions

Table 1. Canadian emissions inventory for manganese based on data from 1984* (tonnes)

Sector	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	Terr.	Canada	% of total
Industrial Processes:													
manganese-bearing alloy production					576							576	47
primary iron and steel production			6		57	229	6	21	16	2		337	27.5
iron and steel foundries		<1	1	<1	6	29	2	<1	1	1		40	3.3
primary copper and nickel production					<1	<1	<1			<1		<1	<0.1
primary zinc production					<1	<1	<1			<1		<1	<0.1
battery manufacturing						<1	<1					1	0.1
cement manufacturing	<1		<1	<1	4	1	<1	<1	1	<1		7	0.6
metallurgical coke manufacturing			<1			<1		<1		<1		<1	<0.1
non-ferrous alloys					<1	<1						<1	<0.1
welding rods					<1	<1						<1	<0.1
miscellaneous sources													
Fuel Combustion, Stationary Sources:													
power generation	<1	<1	<1	<1	<1	4	<1	4	5	<1	<1	14	1.2
industrial fuel combustion	<1	<1	<1	<1	<1	1	1	<1	<1	<1	<1	3	0.2
commercial fuel combustion	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<0.1
residential fuel combustion	<1	<1	2	<1	<1	<1	<1	<1	1	<1	<1	3	0.2
Fuel Combustion, Transportation Sources:													
gasoline-powered motor vehicles**	4	1	7	7	42	71	10	12	29	27	1	211	17.2
Solid Waste Incineration:													
municipal refuse incineration		<1			3	2				<1		5	0.4
sewage sludge incineration						<1				<1		<1	<0.1
Miscellaneous Sources:													
pesticide application												28	2.3
Total	4	1	17	7	688	338	20	37	53	31	1	1225	100

* Based on data presented in Jaques (1987)

** Assumes that 100% of manganese in MMT is emitted from the tailpipe

Table 2. Dose-Response Relationship, Respirable Mn Dust Cumulative Exposure and Abnormal Psychomotor Performance‡

	control	quartile 1	quartile 2	quartile 3	quartile 4	total
N[a]	101	23	23	23	23	92
LIRD,[b] integrated respirable dust, □g/m^3-years	--	264	647	1277	2606	793
range	--	40-516	516-859	902-1665	1729-4433	40-4433
average # of years[c]	--	2.6	3.3	5.9	8.9	5.3
adjusted integrated exposure,[d] □g/m^3	--	101.5	196.1	216.4	292.3	201.6
VRT[e] % (# of individuals)	**1** (1/101) (p=1.0)[h]	**4.3** (1/23) (p=0.34) n.s.	**8.7** (2/23) (p=0.09) n.s.	**0** (0/23) (p=1.0) n.s.	**17.4** (4/23) (p=0.004) *	**7.6** (7/92) *
EHC[f] % (# of individuals)	**5** (5/101) (p=1.0)	**8.7** (2/23) (p=0.6) n.s.	**43.5** (10/23) (p<0.001) *	**13.0** (3/23) (p=0.17) n.s.	**26.1** (6/23) (p=0.005) *	**22.8** (21/92) *
HST[g] % (# of individuals)	**4** (4/101) (p=1.0)	**4.3** (1/23) (p<1.0) n.s.	**8.7** (2/23) (p=0.31) n.s.	**17.4** (4/23) (p=0.038) *	**21.7** (5/23) (p=0.01) *	**13.0** (12/92) *
2 or more, % (# of individuals)	**1** (1/101) (p=1.0)	**0** (0/23) (p=1.0) n.s.	**8.7** (2/23) (p=0.09) n.s.	**8.7** (2/23) (p=0.09) n.s.	**26.1** (6/23) (p=0.0001) *	**10.9** (10/92) *

‡ Data from Roels, *et al.*, 1992; Roels, 1993

a N = Number of individuals examined

b LIRD - Lifetime Integrated Respirable Dust

c Average (arithmatic) number of years worked per group

d LIRD converted to an annual average from an 8-hour shift

e VRT - Visual Reaction Time; percent and number of abnormal responses

f EHC - Eye-Hand Coordination; percent and number of abnormal responses

g HST - Hand Steadiness; percent and number of abnormal responses

h Statistical significance tested by Fisher's Exact Test for difference from control

* Statistically significant at level indicated

n.s. not significant

Table 3. Population distribution of 24-hour personal exposure measures (PEM) and stationary ambient measures (SAM) of PM10 manganese in Riverside, California.

percentile	PEM (ug Mn/m3)	SAM (ug Mn/m3)	PEM measure:SAM arithmetic mean
1	0.010	0.012	0.22
2	0.012	0.013	0.27
5	0.014	0.018	0.31
10	0.016	0.023	0.36
16	0.020	0.026	0.44
25	0.022	0.030	0.49
50	0.035	0.041	0.78
75	0.056	0.055	1.24
84	0.069	0.063	1.53
90	0.082	0.068	1.82
95	0.103	0.078	2.29
98	0.145	0.098	3.22
99	0.212	0.129	4.71
99.5	0.241	0.216	5.36
arithmetic mean	0.045	0.045	1.00

Based on original data provided by Wallace (1994)

Table 4. Annual (1992) ambient air PM10 Mn concentrations

measure	Ambient Mn measurements (ug/m3)			
	St. John	Montreal 2	Hamilton 4	Sault Ste. Marie 2
arithmetic mean	0.011	0.025	0.100	0.158
90th %	0.021	0.034	0.230	0.440
99th %	0.024	0.041	0.370	0.832

Based on data in OMOEE (1993) and original data from Dann (1994)

Table 5. Inhalation exposure to PM10 manganese based on ambient monitoring data

measure	0-6 months**				7months-4 years***				5-11 years****				12-19 years*****				20+ years ******			
	SJ^	MTL^	HAM^	SSM^	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM
uptake* (ug/day)																				
ar. x	0.013	0.030	0.120	0.190	0.033	0.075	0.300	0.474	0.079	0.180	0.720	1.138	0.139	0.315	1.260	1.991	0.152	0.345	1.380	2.180
90th %	0.025	0.041	0.276	0.528	0.063	0.102	0.690	1.320	0.151	0.245	1.656	3.168	0.265	0.428	2.898	5.544	0.290	0.469	3.174	6.072
99th %	0.029	0.049	0.444	0.998	0.072	0.123	1.110	2.496	0.173	0.295	2.664	5.990	0.302	0.517	4.662	10.483	0.331	0.566	5.106	11.482
uptake* (ug/kg bw/day)																				
ar. x	0.002	0.004	0.017	0.027	0.003	0.006	0.023	0.036	0.003	0.007	0.027	0.042	0.002	0.006	0.022	0.035	0.002	0.005	0.020	0.031
90th %	0.004	0.006	0.039	0.075	0.005	0.008	0.053	0.102	0.006	0.009	0.061	0.117	0.005	0.008	0.051	0.097	0.004	0.007	0.045	0.087
99th %	0.004	0.007	0.063	0.143	0.006	0.009	0.085	0.192	0.006	0.011	0.099	0.222	0.005	0.009	0.082	0.184	0.005	0.008	0.073	0.164

^: SJ=St. John; MTL=Montreal; HAM=Hamilton; SSM=Sault Ste. Marie

* : assuming 60% deposition in the pulmonary region, and 100% absorption of manganese deposited in the pulmonary region

** : assuming air intake of 2 m3/day and body weight of 7 kg (Health Canada 1994)

*** : assuming air intake of 5 m3/day and body weight of 13 kg (Health Canada 1994)

**** : assuming air intake of 12 m3/day and body weight of 27 kg (Health Canada 1994)

***** : assuming air intake of 21 m3/day and body weight of 57 kg (Health Canada 1994)

****** : assuming air intake of 23 m3/day and body weight of 70 kg (Health Canada 1994)

Table 6. Estimates of population personal exposure for 1992 based on extrapolation from PTEAM data

measure	Mn personal exposure levels (ug/m3)			
	St. John	Montreal 2	Hamilton 4	Sault Ste. Marie 2
arithmetic mean	0.011	0.025	0.100	0.158
90th %	0.020	0.046	0.183	0.289
99th %	0.052	0.118	0.473	0.747

Table 7. Inhalation exposure to PM10 manganese based on estimates of personal exposure derived from the PTEAM study

measure	0-6 months **				7months-4 years***				5-11 years ****				12-19 years*****				20+ years ******			
	SJ^	MTL^	HAM^	SSM^	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM
uptake* (ug/day)																				
ar. x	0.013	0.030	0.120	0.190	0.033	0.075	0.300	0.474	0.079	0.180	0.720	1.138	0.139	0.315	1.260	1.991	0.152	0.345	1.380	2.180
90th %	0.024	0.055	0.220	0.347	0.060	0.137	0.549	0.867	0.145	0.329	1.318	2.082	0.254	0.576	2.306	3.643	0.278	0.631	2.525	3.990
99th %	0.062	0.142	0.568	0.897	0.156	0.355	1.419	2.242	0.375	0.851	3.406	5.381	0.656	1.490	5.960	9.416	0.718	1.632	6.527	10.313
uptake* (ug/kg bw/day)																				
ar. x	0.002	0.004	0.017	0.027	0.003	0.006	0.023	0.036	0.003	0.007	0.027	0.042	0.002	0.006	0.022	0.035	0.002	0.005	0.020	0.031
90th %	0.003	0.008	0.031	0.050	0.005	0.011	0.042	0.067	0.005	0.012	0.049	0.077	0.004	0.010	0.040	0.064	0.004	0.009	0.036	0.057
99th %	0.009	0.020	0.081	0.128	0.012	0.027	0.109	0.172	0.014	0.032	0.126	0.199	0.012	0.026	0.105	0.165	0.010	0.023	0.093	0.147

^: SJ=St. John; MTL=Montreal; HAM=Hamilton; SSM=Sault Ste. Marie

* : assuming 60% deposition in the pulmonary region, and 100% absorption of manganese deposited in the pulmonary region

** : assuming air intake of 2 m3/day and body weight of 7 kg (Health Canada 1994)

*** : assuming air intake of 5 m3/day and body weight of 13 kg (Health Canada 1994)

**** : assuming air intake of 12 m3/day and body weight of 27 kg (Health Canada 1994)

***** : assuming air intake of 21 m3/day and body weight of 57 kg (Health Canada 1994)

****** : assuming air intake of 23 m3/day and body weight of 70 kg (Health Canada 1994)

Table 8. Daily dietary manganese intakes reported in the literature

Age Group	Daily Mn Intake (mg/day)	Country	Reference
average adult	4.1	Canada	Méranger and Smith 1972
average adult	2.93	Canada (Winnipeg)	Kirkpatrick and Coffin 1977
adult pre-menopausal women	3.1	Canada	Gibson and Scythes 1982
elderly women	3.8	Canada	Gibson *et al.* 1985a
0-6 months	0.47-1.04	Canada	Kirkpatrick *et al.* 1980
6-12 months	1.25-1.68		
22 months	1.5	Canada	Gibson *et al.* 1985b
blue-collar workers	3.7	Canada (Montréal)	Loranger and Zayed 1994
garage mechanics	2.9		
6-11 months	1.11	U.S.A.	Pennington *et al* 1989
2 years	1.50		
14-16 years, females	1.79		
14-16 years, males	2.79		
25-30 years, females	2.12		
25-30 years, males	2.80		
60-65 years, females	2.20		
60-65 years, males	2.63		
adult males	3.4	U.S.A.	Patterson *et al.* 1984
adult females	2.7		
1-4 years	1.29	U.S.A. (Mass.)	Stanek *et al.* 1988
national average	4.02	Britain	Lewis and Buss 1988
average adult	4.6	Britain	Wenlock *et al.* 1979
average adult	3.7	Sweden	Becker and Kumpulainen 1991
adult	2.6	Belgium	Buchet *et al.* 1983
9 months infant	1.06	Australia	Fardy *et al.* 1992
2 years	2.11		
12.5 years, females	3.91		
12.5 years, males	5.08		
adult, females	2.96		
adult, males	5.53		
1-3 months (breastfed)	0.003-0.004	Finland	Vuori 1979

Table 9. Daily manganese consumption derived from individual foodstuffs

Foodstuff	Mn content	Mean consumption of foodstuffs (g/day)					Mean consumption of Mn (mg/day)					Percentage of total Mn derived from foodgroup				
	(mg/100 g)	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+
DAIRY PRODUCTS																
milk, whole	0.004	274.16	377.88	323.16	255.65	138.24	0.011	0.015	0.013	0.010	0.006	1.662	0.876	0.481	0.343	0.157
milk,2%	0.002	188.60	194.50	185.61	194.75	60.64	0.004	0.004	0.004	0.004	0.001	0.572	0.225	0.138	0.130	0.034
milk, skim	0.002	21.20	59.67	55.57	72.56	30.83	0.000	0.001	0.001	0.001	0.001	0.064	0.069	0.041	0.049	0.017
evap. milk, can.	0.006	59.78	12.04	6.54	7.06	11.46	0.004	0.001	0.000	0.000	0.001	0.543	0.042	0.015	0.014	0.019
cream, 10-12% bf	0.001	0.00	1.63	2.83	2.65	10.19	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001	0.001	0.003
ice cream	0.006	1.37	15.35	25.59	25.78	12.80	0.000	0.001	0.002	0.002	0.001	0.012	0.053	0.057	0.052	0.022
yogurt	0.004	0.00	0.78	0.48	0.87	1.54	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.001	0.001	0.002
cheese, cheddar	0.01	0.11	2.56	3.18	5.66	8.33	0.000	0.000	0.000	0.001	0.001	0.002	0.015	0.012	0.019	0.024
cheese, cottage	0.003	0.00	1.73	1.33	1.74	5.35	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.001	0.002	0.005
cheese, proc. cheddar	0.015	0.06	3.59	4.92	6.43	3.81	0.000	0.001	0.001	0.001	0.001	0.001	0.031	0.027	0.032	0.016
butter	0.004	0.73	7.06	12.94	16.67	13.61	0.000	0.000	0.001	0.001	0.001	0.004	0.016	0.019	0.022	0.015
~~TOTAL DAIRY PRODUCTS~~		546.0	676.8	622.2	589.8	298.8	0.019	0.023	0.021	0.020	0.011	2.881	1.334	0.794	0.685	0.314
CEREAL & GRAIN PRODUCTS																
bread, white [US]	0.432	2.12	34.00	76.80	94.88	67.45	0.009	0.147	0.332	0.410	0.291	1.388	8.512	12.347	13.731	8.255
bread, wholewheat & rye [US]	1.561	0.00	5.49	6.47	7.43	19.76	0.000	0.086	0.101	0.116	0.308	0.000	4.966	3.759	3.885	8.736
rolls and biscuits [US]	0.43	0.00	3.64	11.63	15.92	10.00	0.000	0.016	0.050	0.068	0.043	0.000	0.907	1.861	2.293	1.218
flour, wheat	2.24	0.28	3.86	10.38	5.17	6.93	0.006	0.086	0.233	0.116	0.155	0.950	5.010	8.653	3.880	4.396
cake [US]	0.285	0.19	8.59	25.62	42.52	20.37	0.001	0.024	0.073	0.121	0.058	0.082	1.419	2.717	4.060	1.645
cookies	0.46	1.50	18.87	26.00	23.06	15.58	0.007	0.087	0.120	0.106	0.072	1.045	5.030	4.451	3.557	2.030
danish and donuts [US]	0.36	0.00	3.60	5.39	9.53	5.49	0.000	0.013	0.019	0.034	0.020	0.000	0.751	0.722	1.149	0.560
crackers [US]	0.724	0.04	4.83	5.14	5.67	3.45	0.000	0.035	0.037	0.041	0.025	0.044	2.026	1.385	1.375	0.708
pancakes [US]	0.367	0.00	2.16	2.93	3.37	2.04	0.000	0.008	0.011	0.012	0.007	0.000	0.458	0.400	0.414	0.212
cereals, cooked wheat [US]	0.52	13.50	13.94	5.72	4.73	6.53	0.070	0.072	0.030	0.025	0.034	10.637	4.201	1.107	0.824	0.962
cereals, oatmeal	0.585	33.12	20.86	19.95	12.26	16.44	0.194	0.122	0.117	0.072	0.096	29.357	7.072	4.343	2.403	2.725
cereals, corn	0.35	1.07	3.42	5.37	3.40	1.82	0.004	0.012	0.019	0.012	0.006	0.567	0.694	0.699	0.399	0.180
cereals wheat and bran	4.51	0.09	3.37	3.37	3.35	2.31	0.004	0.152	0.152	0.151	0.104	0.615	8.807	5.656	5.061	2.951
rice	0.53	0.00	6.73	13.98	14.56	15.14	0.000	0.036	0.074	0.077	0.080	0.000	2.067	2.757	2.585	2.273
pasta, ordinary	0.28	0.00	10.85	26.24	10.32	13.47	0.000	0.030	0.073	0.029	0.038	0.000	1.760	2.734	0.966	1.068
muffins [US]	0.5	0.00	0.39	0.53	2.12	1.56	0.000	0.002	0.003	0.011	0.008	0.000	0.113	0.099	0.355	0.221
~~TOTAL CEREALS AND GRAINS~~		51.9	144.6	245.5	258.3	208.3	0.295	0.928	1.443	1.401	1.346	44.865	53.795	53.691	46.939	36.144
MEATS/POULTRY/EGGS																
beef, steak	0.014	0.07	3.09	7.37	10.89	17.38	0.000	0.000	0.001	0.002	0.002	0.001	0.025	0.038	0.051	0.069
beef, roast & stewing	0.016	0.27	6.49	12.21	23.27	27.00	0.000	0.001	0.002	0.004	0.004	0.007	0.060	0.073	0.125	0.122
beef, hamburg, reg.	0.017	31.36	20.05	19.23	30.84	21.61	0.005	0.003	0.003	0.005	0.004	0.808	0.198	0.122	0.176	0.104
veal	0.036	0.00	0.50	0.33	1.79	2.16	0.000	0.000	0.000	0.001	0.001	0.000	0.010	0.004	0.022	0.022
pork, fresh	0.02	0.00	7.24	11.96	22.74	22.73	0.000	0.001	0.002	0.005	0.005	0.000	0.084	0.089	0.152	0.129
pork, cured	0.03	0.00	1.95	3.96	4.40	7.78	0.000	0.001	0.001	0.001	0.002	0.000	0.034	0.044	0.044	0.066
lamb	0.022	0.00	0.03	1.80	1.20	0.78	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.015	0.009	0.005
chicken & turkey	0.02	0.00	13.24	16.72	20.32	21.17	0.000	0.003	0.003	0.004	0.004	0.000	0.153	0.124	0.136	0.120
eggs	0.004	4.67	24.16	21.05	21.50	32.29	0.000	0.001	0.001	0.001	0.001	0.028	0.056	0.031	0.029	0.037
liver, kidneys	0.181	0.00	0.91	1.85	2.27	2.81	0.000	0.002	0.003	0.004	0.005	0.000	0.095	0.125	0.138	0.144
cold cuts, fresh [a691.758]	0.04	0.00	5.72	7.85	11.27	9.27	0.000	0.002	0.003	0.005	0.004	0.000	0.133	0.117	0.151	0.105
luncheon meats, canned	0.037	0.00	0.88	0.97	2.20	2.10	0.000	0.000	0.000	0.001	0.001	0.000	0.019	0.013	0.027	0.022
weiners,fresh/canned	0.016	0.00	2.26	6.35	5.45	2.41	0.000	0.000	0.001	0.001	0.000	0.000	0.021	0.038	0.029	0.011
~~TOTAL MEAT/POULTRY/EGGS~~		36.4	86.5	111.7	158.1	169.5	0.006	0.015	0.022	0.032	0.034	0.844	0.889	0.834	1.089	0.956

Table 9 (cont'd). Daily manganese consumption derived from individual foodstuffs

Foodstuff	Mn content (mg/100 g)	Mean consumption of foodstuffs (g/day)					Mean consumption of Mn (mg/day)					Percentage of total Mn derived from foodgroup				
		0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+
FISH /SHELLFISH																
F/F marine fish	0.083	0.50	1.52	4.81	5.00	6.59	0.000	0.001	0.003	0.003	0.004	0.048	0.055	0.113	0.106	0.118
F/F freshwater fish	0.458	0.00	1.12	1.08	1.09	1.26	0.000	0.005	0.005	0.005	0.006	0.000	0.297	0.184	0.167	0.163
canned fish	0.049	0.00	0.43	1.84	4.13	4.07	0.000	0.000	0.001	0.002	0.002	0.000	0.012	0.034	0.068	0.056
F/F shellfish	1.106	0.00	0.28	0.64	1.00	1.93	0.000	0.003	0.007	0.011	0.021	0.000	0.179	0.263	0.371	0.605
TOTAL FISH/SHELLFISH		0.5	3.4	8.4	11.2	13.9	0.000	0.009	0.016	0.021	0.033	0.048	0.544	0.594	0.711	0.942
MIXED DISHES																
soups, meat, canned	0.14	3.37	39.23	42.77	35.94	54.76	0.005	0.055	0.060	0.050	0.077	0.715	3.183	2.228	1.686	2.172
soups, pea, canned	0.25	1.09	14.52	19.97	37.58	30.41	0.003	0.036	0.050	0.094	0.076	0.413	2.104	1.858	3.147	2.154
soups, tomato canned	0.102	0.37	7.70	11.66	7.39	7.02	0.000	0.008	0.012	0.008	0.007	0.057	0.455	0.443	0.253	0.203
soups, dehydrated	0.079	0.00	10.02	7.98	7.92	7.65	0.000	0.008	0.006	0.006	0.006	0.000	0.459	0.235	0.210	0.171
pie, apple	0.2	0.00	2.02	3.87	3.71	9.25	0.000	0.004	0.008	0.007	0.019	0.000	0.234	0.288	0.249	0.524
pie, other	0.21	0.08	3.68	10.35	10.77	11.70	0.000	0.008	0.022	0.023	0.025	0.025	0.448	0.809	0.758	0.696
pizza	0.22	0.00	0.12	3.09	5.09	1.74	0.000	0.000	0.007	0.011	0.004	0.000	0.015	0.253	0.375	0.108
pasta, mixed dishes [US]	0.164	0.00	17.67	36.90	46.99	15.81	0.000	0.029	0.061	0.077	0.026	0.000	1.679	2.252	2.582	0.735
TOTAL MIXED DISHES		4.9	95.0	136.6	155.4	138.3	0.008	0.148	0.225	0.276	0.239	1.210	8.577	8.385	9.258	6.763
ROOT VEGETABLES																
potatoes, raw	0.263	0.00	0.25	0.00	0.00	0.04	0.000	0.001	0.000	0.000	0.000	0.000	0.038	0.000	0.000	0.003
potatoes, baked	0.229	0.00	2.08	2.95	3.05	4.92	0.000	0.005	0.007	0.007	0.011	0.000	0.278	0.251	0.234	0.319
potatoes boiled, skins on	0.14	0.00	2.13	1.81	3.54	5.43	0.000	0.003	0.003	0.005	0.008	0.000	0.173	0.094	0.166	0.215
potatoes, boiled, skins off	0.14	7.51	45.22	77.66	100.9	82.11	0.011	0.063	0.109	0.141	0.115	1.593	3.669	4.046	4.736	3.257
potatoes, french fried	0.3	0.01	18.46	22.78	33.02	20.68	0.000	0.055	0.068	0.099	0.062	0.005	3.209	2.543	3.319	1.758
potatoes, chips	0.44	0.00	1.64	5.18	7.81	1.31	0.000	0.007	0.023	0.034	0.006	0.000	0.418	0.848	1.151	0.163
carrots	0.142	1.39	8.14	10.34	11.06	14.19	0.002	0.012	0.015	0.016	0.020	0.299	0.670	0.546	0.527	0.571
onions	0.137	0.00	0.89	2.45	3.05	6.15	0.000	0.001	0.003	0.004	0.008	0.000	0.071	0.125	0.140	0.239
rutabagas or turnip [boiled]	0.15	0.58	2.40	3.51	3.29	5.69	0.001	0.004	0.005	0.005	0.009	0.132	0.209	0.196	0.165	0.242
beets [boiled]	0.24	0.00	0.43	1.26	1.00	1.80	0.000	0.001	0.003	0.002	0.004	0.000	0.080	0.113	0.080	0.122
TOTAL ROOT VEGETABLES		9.5	81.6	127.9	166.8	142.3	0.01	0.15	0.24	0.31	0.24	2.03	8.79	8.76	10.52	6.89
VEGETABLES - OTHERS																
corn	0.161	0.56	9.90	17.60	12.02	8.16	0.001	0.016	0.028	0.019	0.013	0.137	0.924	1.055	0.648	0.372
cabbage	0.18	0.00	2.69	5.05	6.21	10.26	0.000	0.005	0.009	0.011	0.018	0.000	0.281	0.338	0.374	0.523
celery	0.102	0.03	1.59	2.43	3.45	8.34	0.000	0.002	0.002	0.004	0.009	0.005	0.094	0.092	0.118	0.241
peppers	0.116	0.00	0.05	0.27	0.43	1.28	0.000	0.000	0.000	0.000	0.001	0.000	0.003	0.012	0.017	0.042
lettuce	0.512	0.00	2.37	4.49	8.21	12.70	0.000	0.012	0.023	0.042	0.065	0.000	0.703	0.856	1.408	1.842
cauliflower	0.203	0.00	0.26	0.11	1.11	1.46	0.000	0.001	0.000	0.002	0.003	0.000	0.031	0.008	0.075	0.084
broccoli	0.229	0.87	0.34	1.34	0.20	2.19	0.002	0.001	0.003	0.000	0.005	0.302	0.045	0.114	0.015	0.142
beans [boiled&drained]	0.294	0.32	2.66	4.27	4.49	6.82	0.001	0.008	0.013	0.013	0.020	0.143	0.453	0.467	0.442	0.568
peas [boiled&drained]	0.525	31.10	6.10	6.09	7.66	9.34	0.163	0.032	0.032	0.040	0.049	24.73	1.856	1.190	1.347	1.389
tomatoes	0.105	0.00	3.19	7.47	11.16	17.90	0.000	0.003	0.008	0.012	0.019	0.000	0.194	0.292	0.393	0.532
tomato juice	0.077	0.00	5.28	4.52	5.64	10.02	0.000	0.004	0.003	0.004	0.008	0.000	0.236	0.130	0.145	0.219
tomatoes:sauce,can.,ketchup	0.18	0.00	4.91	7.15	8.88	6.40	0.000	0.009	0.013	0.016	0.012	0.000	0.512	0.479	0.535	0.326
mushrooms. canned	0.086	0.00	0.47	0.86	2.11	1.63	0.000	0.000	0.001	0.002	0.001	0.000	0.023	0.028	0.061	0.040
cucumbers	0.061	0.00	3.47	8.27	11.27	11.37	0.000	0.002	0.005	0.007	0.007	0.000	0.123	0.188	0.230	0.196
baked beans	0.35	0.00	3.11	7.27	12.14	8.12	0.000	0.011	0.025	0.042	0.028	0.000	0.631	0.947	1.423	0.805
TOTAL VEGETABLES - OTHER		32.9	46.4	77.2	95.0	116.0	0.17	0.11	0.17	0.22	0.26	25.32	6.11	6.19	7.23	7.32

Table 9 (cont'd). Daily manganese consumption derived from individual foodstuffs.

Foodstuff	Mn content	Mean consumption of foodstuffs (g/day)					Mean consumption of Mn (mg/day)					Percentage of total Mn derived from foodgroup				
	(mg/100 g)	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+	0-6 mo.	7mo.-4yrs	5-11yrs	12-19 yrs	20 yrs+
FRUIT PRODUCTS																
citrus fruit - raw	0.021	0.00	11.47	24.70	22.29	33.25	0.000	0.002	0.005	0.005	0.007	0.000	0.140	0.193	0.157	0.198
citrus fruit, canned	0.007	0.00	0.00	0.17	0.04	0.16	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
citrus juice	0.018	3.46	34.61	22.54	32.98	35.01	0.001	0.008	0.004	0.006	0.006	0.094	0.361	0.151	0.199	0.179
citrus juice canned	0.024	11.82	9.69	12.96	11.05	13.38	0.003	0.002	0.003	0.003	0.003	0.430	0.135	0.116	0.089	0.091
apples - raw [skin]	0.045	1.15	26.79	41.38	33.85	20.52	0.001	0.012	0.019	0.015	0.009	0.078	0.699	0.693	0.510	0.262
apple juice, can. unsweet.	0.113	14.98	44.21	26.66	9.65	13.30	0.017	0.050	0.030	0.011	0.015	2.565	2.895	1.121	0.365	0.426
apple sauce, canned	0.075	1.45	3.91	8.81	3.16	5.97	0.001	0.003	0.007	0.002	0.004	0.165	0.170	0.246	0.079	0.127
bananas	0.152	3.25	12.98	21.42	11.19	12.82	0.005	0.020	0.033	0.017	0.019	0.748	1.143	1.212	0.570	0.552
grapes	0.718	0.00	0.82	1.52	2.67	2.94	0.000	0.006	0.011	0.019	0.021	0.000	0.341	0.406	0.642	0.598
grape juice, bottled	0.36	0.00	5.27	2.52	5.02	2.15	0.000	0.019	0.009	0.018	0.008	0.000	1.099	0.338	0.605	0.219
peaches	0.047	0.50	12.25	10.27	6.56	10.17	0.000	0.006	0.005	0.003	0.005	0.036	0.334	0.180	0.103	0.135
pears	0.076	73.53	18.10	6.70	4.06	7.73	0.056	0.014	0.005	0.003	0.006	8.467	0.797	0.189	0.103	0.166
plums/dr.prunes/can.plums	0.13	0.95	2.15	2.72	2.64	4.74	0.001	0.003	0.004	0.003	0.006	0.187	0.162	0.132	0.115	0.175
cherries	0.102	0.00	0.90	1.15	0.88	1.64	0.000	0.001	0.001	0.001	0.002	0.000	0.053	0.044	0.030	0.047
melons	0.034	0.00	1.18	7.39	3.82	9.53	0.000	0.000	0.003	0.001	0.003	0.000	0.023	0.094	0.044	0.092
stawberries	0.29	0.00	3.01	7.56	5.39	7.75	0.000	0.009	0.022	0.016	0.022	0.009	0.506	0.816	0.524	0.637
blueberries	0.282	0.67	0.67	1.00	1.51	1.99	0.002	0.002	0.003	0.004	0.006	0.286	0.109	0.105	0.143	0.159
pineapple	1.65	0.00	0.70	1.68	1.66	2.22	0.000	0.012	0.028	0.027	0.037	0.000	0.669	1.032	0.918	1.038
raisins	0.29	0.00	0.50	0.53	1.08	0.62	0.000	0.001	0.002	0.003	0.002	0.000	0.084	0.057	0.105	0.051
TOTAL FRUIT PRODUCTS		111.8	189.2	201.7	159.5	185.9	0.086	0.168	0.191	0.158	0.182	13.05	9.721	7.123	5.301	5.151
FATS & OILS																
cooking fats & salad oils [US]	0.002	0.00	1.23	2.21	3.97	4.95	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.002	0.003	0.003
margarine [U.S.]	0.002	0.02	2.65	6.13	8.34	6.23	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.005	0.006	0.004
peanut butter & peanuts	1.88	0.16	2.98	6.08	6.60	3.52	0.003	0.056	0.114	0.124	0.086	0.456	3.247	4.254	4.157	1.875
TOTAL FATS AND OILS		0.180	6.860	14.420	18.910	14.700	0.003	0.056	0.114	0.124	0.086	0.458	3.251	4.260	4.165	1.881
FOODS, PRIMARILY SUGAR																
sugar, white	0.007	1.54	7.08	11.66	14.46	19.20	0.000	0.000	0.001	0.001	0.001	0.016	0.029	0.030	0.034	0.038
syrup	1.7	3.13	2.89	6.45	5.59	4.94	0.053	0.049	0.110	0.095	0.084	8.062	2.847	4.081	3.184	2.379
jams	0.09	0.28	3.55	6.76	9.63	6.14	0.000	0.003	0.006	0.009	0.006	0.038	0.185	0.226	0.290	0.157
honey	0.08	1.30	0.86	2.02	1.88	2.17	0.001	0.001	0.002	0.002	0.002	0.158	0.040	0.060	0.050	0.049
puddings	0.037	18.13	13.16	8.85	10.59	8.78	0.007	0.005	0.003	0.004	0.003	1.016	0.282	0.122	0.131	0.092
candy, chocolate bars	0.47	0.16	3.14	5.45	8.10	3.58	0.001	0.015	0.026	0.038	0.017	0.114	0.855	0.953	1.275	0.477
candy, others	0.086	0.01	5.36	8.47	10.39	4.58	0.000	0.005	0.007	0.009	0.004	0.001	0.267	0.271	0.299	0.112
gelatin dessert	0.003	0.09	9.59	7.49	5.98	7.80	0.000	0.000	0.000	0.000	0.000	0.000	0.017	0.008	0.008	0.007
TOTAL FOODS/SUGARS		24.640	45.630	57.150	66.620	57.190	0.062	0.078	0.155	0.157	0.117	9.406	4.522	5.752	5.270	3.310
NON-ALCOHOLIC DRINKS																
coffee	0.027	0.00	6.48	11.99	83.95	347.77	0.000	0.002	0.003	0.023	0.094	0.000	0.101	0.120	0.759	2.660
tea	0.219	0.00	8.47	22.20	81.64	354.13	0.000	0.019	0.049	0.179	0.776	0.000	1.075	1.809	5.990	21.971
soft drinks	0.022	2.39	100.33	193.57	240.70	109.91	0.001	0.022	0.043	0.053	0.024	0.080	1.279	1.585	1.774	0.686
TOTAL NON-ALCOHOLIC DRINKS		2.390	115.280	227.760	406.290	811.810	0.001	0.042	0.094	0.254	0.894	0.080	2.455	3.515	8.523	25.318
ALCOHOLIC DRINKS																
wine	0.39	0.00	0.02	0.73	1.84	23.54	0.000	0.000	0.003	0.007	0.092	0.000	0.005	0.106	0.240	2.601
beer	0.012	0.00	1.22	1.93	21.44	121.05	0.000	0.000	0.000	0.003	0.015	0.000	0.008	0.009	0.086	0.412
TOTAL ALCOHOLIC DRINKS		0.000	1.240	2.660	23.280	144.590	0.000	0.000	0.003	0.010	0.106	0.000	0.013	0.115	0.327	3.012
GRAND TOTAL		921.040	1492.470	1833.100	2108.280	2299.310	0.660	1.726	2.687	2.985	3.530	100.000	100.000	100.000	100.000	100.000

Table 10. Canadian dietary manganese intake for different age groups, and different infant diets.

age class	Mn concentration in food (mg/100 g)	Consumption (g/day)	Mn intake (mg/day)
0-6 months, exclusively breastfed	0.002*	750	0.000
0-6 months, fed exclusively milk-based formula	0.010**	750	0.000
0-6 months, fed exclusively soya-based formula	0.063**	750	0.000
0-6 months***			0.660
7 months - 4 years***			1.726
5 - 11 years***			2.687
12 - 19 years***			2.985
20 years +***			3.530

* Vaughan et al 1979

**Dabeka and McKenzie 1992

***based on data derived in Table 9

Table 11. Ingestion of manganese through food, water and soil.

ingestion source	**0-6 months ,breast-fed**				**0-6 months, milk-based formula**				**0-6 months, soya-based formula**				**0-6 months**			
	SJ*	**MTL***	**HAM***	**SSM***	**SJ**	**MTL**	**HAM**	**SSM**	**SJ**	**MTL**	**HAM**	**SSM**	**SJ**	**MTL**	**HAM**	**SSM**
dietary Mn (mg/day)	0.015	0.015	0.015	0.015	0.075	0.075	0.075	0.075	0.473	0.473	0.473	0.473	0.660	0.660	0.660	0.660
Mn in drinking H2O (mg/l)	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100
consumption (l/day)	0.000	0.000	0.000	0.000	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750
drinking H2O Mn (mg/day)	0.000	0.000	0.000	0.000	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075	0.075
Mn in soil (mg/g)	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500
ingestion (g/day)	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035
soil Mn (mg/day)	0.018	0.018	0.088	0.088	0.018	0.018	0.088	0.088	0.018	0.018	0.088	0.088	0.018	0.018	0.088	0.088
total Mn ingested (mg/day)	**0.033**	**0.033**	**0.103**	**0.103**	**0.168**	**0.168**	**0.238**	**0.238**	**0.566**	**0.566**	**0.636**	**0.636**	**0.753**	**0.753**	**0.823**	**0.823**
intestinal absorption (fraction)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
total Mn absorbed (mg/day)	0.033	0.033	0.103	0.103	0.168	0.168	0.238	0.238	0.566	0.566	0.636	0.636	0.753	0.753	0.823	0.823
total Mn absorbed (ug/day)	33.2	33.2	102.5	102.5	168.2	168.2	237.5	237.5	566.2	566.2	635.5	635.5	753.2	753.2	822.5	822.5
biliary excretion (fraction)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
manganese uptake (ug/day)	**33.2**	**33.2**	**102.5**	**102.5**	**168.2**	**168.2**	**237.5**	**237.5**	**566.2**	**566.2**	**635.5**	**635.5**	**753.2**	**753.2**	**822.5**	**822.5**
manganese uptake (ug/kg bw/day)	**4.7**	**4.7**	**14.6**	**14.6**	**24.0**	**24.0**	**33.9**	**33.9**	**80.9**	**80.9**	**90.8**	**90.8**	**107.6**	**107.6**	**117.5**	**117.5**

ingestion source	**7 months - 4 years**				**5-11 years**				**12-19 years**				**+20 years**			
	SJ	**MTL**	**HAM**	**SSM**	**SJ**	**MTL**	**HAM**	**SSM**	**SJ**	**MTL**	**HAM**	**SSM**	**SJ**	**MTL**	**HAM**	**SSM**
dietary Mn (mg/day)	1.726	1.726	1.726	1.726	2.687	2.687	2.687	2.687	2.985	2.985	2.985	2.985	3.530	3.530	3.530	3.530
Mn in drinking H2O (mg/l)	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100
consumption (l/day)	0.800	0.800	0.800	0.800	0.900	0.900	0.900	0.900	1.300	1.300	1.300	1.300	1.500	1.500	1.500	1.500
drinking H2O Mn (mg/day)	0.080	0.080	0.080	0.080	0.090	0.090	0.090	0.090	0.130	0.130	0.130	0.130	0.150	0.150	0.150	0.150
Mn in soil (mg/g)	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500	0.520	0.520	2.500	2.500
ingestion (g/day)	0.050	0.050	0.050	0.050	0.035	0.035	0.035	0.035	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020
soil Mn (mg/day)	0.026	0.026	0.125	0.125	0.018	0.018	0.088	0.088	0.010	0.010	0.050	0.050	0.010	0.010	0.050	0.050
total Mn ingested (mg/day)	**1.832**	**1.832**	**1.931**	**1.931**	**2.795**	**2.795**	**2.865**	**2.865**	**3.125**	**3.125**	**3.165**	**3.165**	**3.690**	**3.690**	**3.730**	**3.730**
intestinal absorption (fraction)	0.1	0.1	0.1	0.1	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
total Mn absorbed (mg/day)	0.183	0.183	0.193	0.193	0.140	0.140	0.143	0.143	0.156	0.156	0.158	0.158	0.185	0.185	0.187	0.187
total Mn absorbed (ug/day)	183.2	183.2	193.1	193.1	139.76	139.76	143.22	143.22	156.27	156.27	158.25	158.25	184.52	184.52	186.5	186.5
biliary excretion (fraction)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
manganese uptake (ug/day)	**54.96**	**54.96**	**57.93**	**57.93**	**41.928**	**41.928**	**42.967**	**42.967**	**46.881**	**46.881**	**47.475**	**47.475**	**55.356**	**55.356**	**55.95**	**55.95**
manganese uptake (ug/kg bw/day)	**4.2**	**4.2**	**4.5**	**4.5**	**1.6**	**1.6**	**1.6**	**1.6**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**

*SJ=St. John; MTL=Montreal; HAM=Hamilton; SSM=Sault Ste. Marie

Table 12 . Total manganese uptake from all sources (inhalation exposure based on ambient monitoring data)

measure	0-6 months, breast-fed				0-6 months, milk formula				0-6 months, soya formula				0-6 months, CEPA foods			
	SJ^	MTL^	HAM^	SSM^	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM
total Mn uptake (ug/day)																
mean	**33.21**	**33.23**	**102.62**	**102.69**	**168.21**	**168.23**	**237.62**	**237.69**	**566.21**	**566.23**	**635.62**	**635.69**	**753.21**	**753.23**	**822.62**	**822.69**
90th %*	33.23	33.24	102.78	103.03	168.23	168.24	237.78	238.03	566.23	566.24	635.78	636.03	753.23	753.24	822.78	823.03
99th %*	33.23	33.25	102.94	103.50	168.23	168.25	237.94	238.50	566.23	566.25	635.94	636.50	753.23	753.25	822.94	823.50
total Mn uptake (ug/kg bw/day)																
mean	**4.74**	**4.75**	**14.66**	**14.67**	**24.03**	**24.03**	**33.95**	**33.96**	**80.89**	**80.89**	**90.80**	**90.81**	**107.60**	**107.60**	**117.52**	**117.53**
90th %	4.75	4.75	14.68	14.72	24.03	24.03	33.97	34.00	80.89	80.89	90.83	90.86	107.60	107.61	117.54	117.58
99th %	4.75	4.75	14.71	14.79	24.03	24.04	33.99	34.07	80.89	80.89	90.85	90.93	107.60	107.61	117.56	117.64

measure	7 months-4 years				5-11 years				12-19 years				20 + years			
	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM
total Mn uptake (ug/day)																
mean	**54.99**	**55.04**	**58.23**	**58.40**	**42.01**	**42.11**	**43.69**	**44.11**	**47.02**	**47.20**	**48.74**	**49.47**	**55.51**	**55.70**	**57.33**	**58.13**
90th %	55.02	55.06	58.62	59.25	42.08	42.17	44.62	46.14	47.15	47.31	50.37	53.02	55.65	55.83	59.12	62.02
99th %	55.03	55.08	59.04	60.43	42.10	42.22	45.63	48.96	47.18	47.40	52.14	57.96	55.69	55.92	61.06	67.43
total Mn uptake (ug/kg bw/day)																
mean	**4.23**	**4.23**	**4.48**	**4.49**	**1.56**	**1.56**	**1.62**	**1.63**	**0.82**	**0.83**	**0.86**	**0.87**	**0.79**	**0.80**	**0.82**	**0.83**
90th%	4.23	4.24	4.51	4.56	1.56	1.56	1.65	1.71	0.83	0.83	0.88	0.93	0.79	0.80	0.84	0.89
99th %	4.23	4.24	4.54	4.65	1.56	1.56	1.69	1.81	0.83	0.83	0.91	1.02	0.80	0.80	0.87	0.96

^SJ=St. John; MTL=Montreal; HAM=Hamilton; SSM=Sault Ste. Marie

* Percentiles refer to percentiles of inhalation exposure; no population distribution was used for ingestion sources.

Table 13. Fractional manganese uptake from air (based on ambient data), food, water and soil.

measure	0-6 months, breast-fed				7 months-4 years				5-11 years				12-19 years				20 + years			
	SJ^	MTL^	HAM^	SSM^	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM	SJ	MTL	HAM	SSM
total Mn uptake (ug/day)																				
mean	33.21	33.23	102.62	102.69	54.99	55.04	58.23	58.40	42.01	42.11	43.69	44.11	47.02	47.20	48.74	49.47	55.51	55.70	57.33	58.13
air uptake/total Mn uptake (percent)																				
mean	0.04	0.09	0.12	0.18	0.06	0.14	0.52	0.81	0.19	0.43	1.65	2.58	0.29	0.67	2.59	4.02	0.27	0.62	2.41	3.75
food uptake/total Mn uptake (percent)																				
mean	45.16	45.14	14.62	14.61	94.16	94.09	88.92	88.66	95.96	95.73	92.27	91.40	95.24	94.88	91.88	90.53	95.39	95.06	92.36	91.09
drinking water uptake/total Mn uptake (percent)																				
mean	0.00	0.00	0.00	0.00	4.36	4.36	4.12	4.11	3.21	3.21	3.09	3.06	4.15	4.13	4.00	3.94	4.05	4.04	3.92	3.87
soil uptake/total Mn uptake (percent)																				
mean	54.20	54.17	85.75	85.70	1.42	1.42	6.44	6.42	0.64	0.64	3.02	2.99	0.32	0.32	1.54	1.52	0.27	0.27	1.31	1.29

^ SJ=St. John; MTL=Montreal; HAM=Hamilton; SSM=Sault Ste. Marie

Table 14. Manganese exposure for occupations with high potential inhalation exposure to manganese

route	office workers*	taxi drivers*	garage mechanics**	battery plant workers (Roels 1992, Q1)***	battery plant workers (Roels 1992, Q2)****	battery plant workers (Roels 1992, Q3)*****	battery plant workers (Roels 1992, Q4)******	battery plant workers (Roels 1992, total)*******
24-hr [Mn] in air (ug/m3)	0.01	0.014	0.085	31.54	60.92	67.2	90.8	62.6
inhalation Mn uptake (ug/day)^	**0.138**	**0.1932**	**1.173**	**435.252**	**840.696**	**927.36**	**1253.04**	**863.88**
inhalation Mn uptake (ug/kg bw/day)	**0.002**	**0.003**	**0.017**	**6.218**	**12.010**	**13.248**	**17.901**	**12.341**
dietary Mn intake (mg/day)^^	3.53	3.53	3.53	3.53	3.53	3.53	3.53	3.53
drinking H2O Mn intake (mg/day)^^	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
soil Mn intake (mg/day)^^	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
total ingested Mn (mg/day)	3.69	3.69	3.69	3.69	3.69	3.69	3.69	3.69
ingested Mn uptake (ug/day)^^^	**55.35**	**55.35**	**55.35**	**55.35**	**55.35**	**55.35**	**55.35**	**55.35**
total Mn uptake (ug/day)	**55.49**	**55.54**	**56.52**	**490.60**	**896.05**	**982.71**	**1308.39**	**919.23**
total Mn uptake (ug/kg bw/day)	**0.793**	**0.793**	**0.807**	**7.009**	**12.801**	**14.039**	**18.691**	**13.132**
inhalation Mn/total Mn (%)	**0.2**	**0.3**	**2.1**	**88.7**	**93.8**	**94.4**	**95.8**	**94.0**

* inhalation exposure based on 24-hour personal exposure monitoring of respirable Mn (Zayed et al 1994b)

** inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 0.25 ug Mn/m3 (TSP) in an car repair garage (Zayed et al 1994) and off-work exposure of 0.025 ug Mn/m3

*** inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 101.5 ug Mn/m3 and off-work exposure of 0.025 ug Mn/m3

**** inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 196.1 ug Mn/m3 and off-work exposure of 0.025 ug Mn/m3

***** inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 216.4 ug Mn/m3 and off-work exposure of 0.025 ug Mn/m3

****** inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 292.3 ug Mn/m3 and off-work exposure of 0.025 ug Mn/m3

******* inhalation exposure based on at-work exposure (10m3/day, 5 days./week) of 201.6 ug Mn/m3 and off-work exposure of 0.025 ug Mn/m3

^ assuming 60% deposition of PM10 in the pulmonary region and 100% absorption of manganese deposited in the pulmonary region

^^based on data of adult manganese ingestion from food, water and soil presented in Table 11.

^^^assuming 5% absorption across the gastrointestinal tract and 70% biliary excretion (uptake=1.5% of intake)

Table A1. Individual exposure and response data for 92 workers in Roels et al. (1992).

CRD	LIRD	ind. #	VRT	EHC	HST	# yrs.	age
0021	63	15	0	0	0	3.0	39.3
0021	65	77	0	0	0	3.1	31.2
0021	55	66	0	0	0	2.6	27.1
0046	520	52	0	1	1	11.3	40.0
0046	460	60	0	0	0	10.0	37.5
0046	207	84	0	0	0	5.7	39.6
0065	1176	53	0	0	0	7.6	32.8
0065	1390	86	0	0	1	8.4	44.0
0065	256	47	1	0	0	8.0	32.7
0104	1053	16	0	0	0	6.3	26.3
0104	569	38	0	1	0	3.6	24.2
0104	605	28	0	1	0	3.8	29.3
0104	390	27	0	0	0	2.6	26.4
0104	498	62	0	0	1	3.2	24.0
0104	516	4	0	0	0	3.3	32.0
0104	516	11	0	0	0	3.3	29.1
0163	2421	2	0	0	0	12.1	48.2
0163	575	23	0	1	0	3.3	22.6
0163	163	6	0	0	0	1.0	33.3
0163	700	10	0	1	0	4.0	33.4
0163	1309	82	0	0	0	7.4	46.4
0163	718	18	0	0	0	4.1	29.5
0179	1647	34	0	1	0	9.2	49.5
0179	752	51	1	0	0	4.2	31.7
0179	1074	37	0	0	0	6.0	31.5
0179	2685	61	0	0	1	15.0	39.5
0179	1844	41	0	0	0	10.3	36.3
0179	627	56	0	0	0	3.5	23.8
0179	806	44	0	0	0	4.5	27.6
0179	1450	48	0	0	0	8.1	27.4
0179	1665	1	0	0	0	9.3	34.7

CRD	LIRD	ind. #	VRT	EHC	HST	# yrs.	age
0179	2506	40	0	0	0	14.0	49.6
0179	752	49	0	0	0	4.2	36.3
0179	430	50	0	0	0	2.4	22.0
0179	1307	19	0	0	0	7.3	29.0
0179	1967	78	0	0	0	10.4	41.2
0179	0527	017	0	0	0	3.5	23.5
0179	609	81	0	1	0	3.4	26.0
0179	1790	3	0	0	0	10.0	32.2
0179	1396	63	0	0	0	7.8	35.7
0179	859	21	0	0	0	4.8	26.7
0179	3162	74	0	0	0	17.7	49.3
0179	1307	65	0	0	0	7.3	29.7
0179	1844	29	0	0	0	10.3	49.0
0179	1110	68	0	0	0	6.2	25.8
0179	1951	26	0	0	0	10.9	33.4
0201	1469	71	0	0	0	7.3	36.7
0201	1328	92	0	0	0	6.6	28.8
0201	604	91	0	0	0	3.0	39.9
0201	624	90	0	0	0	3.1	34.0
0201	2012	46	0	0	0	1.0	35.6
0201	302	14	0	0	0	1.5	36.1
0201	40	20	0	0	0	0.2	22.2
0201	60	22	0	1	0	0.3	22.1
0201	40	12	0	0	0	0.2	22.5
0201	80	42	0	1	0	0.4	23.9
0201	1389	5	0	0	0	6.9	31.1
0201	362	7	0	0	0	1.8	23.1
0201	262	8	0	0	0	1.3	39.0
0201	403	25	0	0	0	2.0	23.4
0243	97	83	0	0	0	0.4	23.5
0243	2911	72	0	0	0	6.7	29.6
0243	3519	39	0	1	1	8.0	31.0
0244	477	88	0	0	0	2.3	24.0

CRD	LIRD	ind.#	VRT	EHC	HST	# yrs.	age
0244	477	33	0	0	0	2.3	24.0
0244	477	69	0	0	0	2.3	23.0
0265	677	32	0	1	0	3.3	23.6
0314	565	85	0	0	0	2,4	22.9
0314	618	35	0	0	1	2,7	22.9
0319	569	67	0	0	0	2.4	22.7
0468	1123	9	0	0	0	2.4	25.3
0468	2668	24	1	1	0	5.7	30.8
0468	2480	31	0	1	1	5.3	30.8
0468	1872	30	0	0	0	4.0	24.6
0468	2380	13	0	0	0	5.0	34.8
0499	902	80	0	0	1	3.4	31.5
0499	750	59	0	1	0	2.4	33.8
0499	768	64	1	1	0	2.5	26.9
0499	578	45	0	1	0	2.0	28.6
0530	977	87	0	0	0	3.5	49.4
0530	941	36	0	0	0	3.3	30.8
0613	2061	70	0	0	0	7.8	29.3
0634	1117	75	0	0	0	3.7	23.8
0796	1082	79	0	1	1	2.6	24.9
0907	3715	43	0	1	1	7.0	32.0
0907	3574	73	1	1	0	6.7	38.3
0907	4433	76	1	0	0	9.4	28.9
0907	1562	58	0	1	1	2.4	36.6
0907	3668	57	0	0	0	6.9	35.7
1201	2651	89	0	0	0	9.1	30.0
1317	1729	55	1	1	1	3.3	25.6
1317	1603	54	0	0	0	2.6	23.8

Figure A1. Exposure and response distribution from Roels et al. 1992